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Original Communications

CONGENITAL SYPHILIS

IN THE LIGHT OF THIRTY YEARS' INVESTIGATION OF THE SPIROCHETE AND TWENTY-FIVE YEARS' EXPERIENCE WITH SALVARSAN*

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Translated by H. A. Haynes, Jr., M.D., Ann Arbor, Mich.

FOREWORD

IT WAS for three reasons that I decided to publish my lectures given in Santander on the problem of congenital syphilis. First, much confusion and misunderstanding remained in spite of Matzenauer's advances (1903) and the definite results of etiologic investigations in Germany since 1905. Newly acquired facts made a new presentation desirable, especially as they can be vouched for from personal experience.

Second, I wished to present the results of German research in other countries for the information of physicians and to clear up misunderstandings which are still hindering the battle against this world epidemic.

And third, I am convinced that today this subject demands closer cooperation between pediatricians, syphilologists, gynecologists, pathologists, and those engaged in other branches of medicine. However, in the successful struggle for the freeing of humanity from the scourge of syphilis, it is especially important to prevent the transmission of the disease, falsely called hereditary syphilis, and thereby free innocent children from the curse of a generalized infection with which they become afflicted even before birth. May this goal soon be reached by every friend of humanity, and may further useful contributions follow this unified presentation. Then, indeed, the elimination of syphilis will no longer be pointed to as Utopian.

Bonn, December 31, 1935.

ERICH HOFFMANN.

*Die Angeborene Syphilis im Lichte 30 jähriger Spirochäten—un 25 jähriger Salvarsanforschung: Abhandlungen aus der Kinderheilkunde un ihren Grenzgebieten, Heft 40, 1936, Berlin, S. Karger.

Lectures given in Spanish (August 12-17, 1935) at the International University at Santander, Spain, in the amphitheater of the Casa de Salud de Valdecilla.

†Professor of Dermatology.

I. INTRODUCTION

THE advances which have been made during the past thirty years in the etiology and experimental investigation of acquired syphilis have become very important in the presentation of the theory of congenital syphilis. In spite of these advances, widespread fallacies exist which have not yet been clarified. As in the field of tuberculosis, famous clinicians and pathologists, such as P. Ricord, R. Virchow, A. Fournier, A. Neisser, endeavored to determine the limits and nature of syphilis before the discovery of its etiologic agent and before satisfactory experimental animals were available. In spite of clinical experience, they reached false conclusions which have persisted and which even today influence some physicians. In both of these chronic and polymorphous diseases, whose differentiation from diseases clinically resembling them was once so difficult, a well-grounded study could begin only after discovery of their etiologic agents. By the introduction of exact methods of investigation Robert Koch, who died twenty-five years ago, first lightened the gloom of tuberculosis with the flame of his genius more than fifty years ago (1882), while only thirty years have passed since the discovery of the spirochete of syphilis (Schaudinn and Hoffmann[1]). By the introduction of experimental syphilis (Metschnikoff-Roux[2]), the serologic reaction (A.v. Wassermann[3]), and spinal fluid diagnosis,[4] valuable supplements were found which, together with the discovery of Fritz Schaudinn, placed us for the first time on a definite basis regarding the recognition of the pathogenesis of congenital syphilis. In connection with proof of the curative and preventive action of atoxyl (P. Uhlenhuth, E. Hoffmann, Salmon, and others), Paul Ehrlich created modern chemical therapy, which, following the introduction of arsenobenzol (1910),[5] has laid the foundation for the prevention of and for an efficient battle against congenital syphilis.

If I review, in four lectures, the greatest advances in a field which is covered by a voluminous literature, it seems to me better to consider more fully the new discoveries of worth rather than the older pathology and symptomatology. These new discoveries have altered our position in regard to this problem and have made us more optimistic, in spite of some erroneous views which have persisted. The time has come to draw

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[1]First discovery March 3, following joint research at the Berliner Hautklinik (Charité), first publication April 25, 1905, in the publication of the Kaiserlichen Gesundheitsamt (see Wien. klin. Wchnschr. 1935, No. 32 and Vorträge und Urkunden, etc., Verlag S. Karger, 1930). Here there is an exact description of the discovery of the etiologic agent of syphilis (Appendix 122-124) as well as a reprint of the first four original articles.

[2]In apes in 1903; in rabbits: Bertarelli and Volpino in the eye in 1906. Parodi in the testicle in 1907, and E. Hoffmann, Löhe and Mulzer in the skin of the testicle in 1908 first found the virus (primary syphiloma).

[3]In 1906, on the basis of the complement fixation reaction of Bordet, in conjunction with A. Neisser and C. Bruck.

[4]After Quincke's discovery of the lumbar puncture, Ravaut, Sicard, and others introduced its use, and Wassermann and Plaut supplemented it by the specific reaction.

[5]Salvarsan in rabbits in 1909 (in collaboration with Bertheim and Hata); in man in 1910; neosalvarsan in 1912.

conclusions, clearly and emphatically, from these advances and to make our goal the elimination of this once dreaded scourge, laying stress on familial and social problems. Many details are to be found in the new Handbuch, in articles by Rietschel, E. Müller, Péhu, Kerl, and others,[6] while as yet the fourth volume of the French work "Traité de la Syphilis"[7] (Jeanselme) has not been published. As the literature is voluminous and many publications are of doubtful value, I believe it better to limit myself to the accepted facts and views which are of practical import for the elimination of congenital syphilis.

Owing to the frequency of transmission of syphilis to the fetus, syphilis has always assumed a special position among the chronic infectious diseases. Premature interruption of pregnancy and expulsion of a macerated fetus are consequences of this disease which have been ascribed to a very early infection, explained by "germinative transmission" and even blastophthoria. This assumption was made by Paracelsus, who wrote in 1529, "Fit morbus hereditarius, et transit a patre ad filium." In a noteworthy manner, Ambroise Paré in 1633 said, "Souvent on voit sortir les petits enfants hors le ventre de leurs mères ayant cette maladie, et tôt après, avoir plusieurs pustules sur leurs corps; lesquels estant ainsi infestés, baillent la vérole à autant de nourrices qui les allaitent."[8]

Such strictly clinical observations explain the choice of the term "hereditary," which was formerly so generally accepted that its exclusion from the terminology of many countries appears to be difficult. Nevertheless, this term should be avoided, because the transmission of the spirochete of syphilis has nothing to do with heredity, the laws of which are now known. Instead, the present term "congenital syphilis" has become fairly generally accepted. Objection has at times been raised to this designation because it suggests infection through conception, and the terms "syphilis innata" and "connatalis" have been suggested to replace "congenital syphilis." I support this change in terminology and E. Müller, Péhu and Kerl have cited the latter names in their new Handbuch articles. Thus I may designate as "syphilis innata" the severe fetal forms now called congenital syphilis in the French literature, and as "syphilis connatalis and postnatalis" the milder forms which first appear after birth. From these diaplacental infections, those infections occurring during and after birth must be distinguished as acquired infant syphilis, "syphilis acquisita infantum," and, as we shall see later, the rarer mixed infection, "syphilis binaria."

[6] In Arzt-Zieler, Haut- und Geschlechtskrankheiten, Urban und Schwarzenberg, 4,541 (bibliography here given).

[7] Now being completed by Sézary (Masson et Cie., Paris, publishers).

[8] Quoted from C. F. Marshall, Syphilology, etc. (London, 1906, p. 317). As Rietschal stated, Fallopia, the personal physician of Popes Alexander I and Julius II, had already recognized the syphilitic fetus and infection of wet nurses (Jadassohn's Handbuch, 19, 1).

II. PATHOGENESIS (METHOD OF TRANSMISSION)

Whether a germinative transmission is possible or whether in syphilis, as in all other infectious diseases, infection becomes established later in the course of pregnancy through the placenta and umbilical cord, is a question of decisive importance in regard to further problems, especially that of prevention. As will be seen below, the course of infection is explained in the latter sense by our investigations. The opposing views of certain physicians, who cannot renounce old familiar and beloved theories, similar to the opposition of Rudolf Virchow to Robert Koch's discovery, cannot seriously oppose the newly won facts.

A. *Theory of Germinative (Paternal) Syphilis.*—The studies of the late Rudolf Matzenauer in 1903, shortly before the discovery of the spirochete, had shaken the theory of paternal syphilis so strongly that many experienced clinicians were already turning from it. Although my teacher, Edmund Lesser, as well as E. Finger and others, strongly supported this theory of paternal transmission, which was contrary to sound reasoning and which confused rather than helped the young physician, I had known it to be incorrect even before Matzenauer's famous publication in Vienna. However, at that time, I refrained from opposing this theory out of consideration for my teacher. Since the discovery of the spirochete, this theory[9] has become entirely untenable.

Because syphilis is usually introduced into the family by the father, the older physicians suspected that a "purely paternal transmission" could occur, thus sparing the mother from the disease, and that the "guilt" of the procreator would be visited on the children (and children's children). This supposition, which was indeed incompatible with the known contagious nature of the virus of syphilis, became strengthened in the minds of clinicians. Before the discovery of the Wassermann reaction, mothers of syphilitic children were at times found to exhibit no symptoms or clinical manifestations of syphilis, even after most thorough examinations. It was already known at that time that the tendency of syphilis was prolonged latency in the early as well as in the late stages. But the entirely asymptomatic course, the "silent infection," was only admitted later after animal experimentation (rabbits) by Kolle and others. Certainly Matzenauer had already referred to it and to the fact that in a series of mothers of definitely syphilitic children, suggestive and even positive signs (adenopathy, leucoderma, essential alopecia, etc.) could be demonstrated by a very thorough clinical examination. This idea of an asymptomatic syphilis later became confirmed by numerous serologic examinations and has given rise to the idea that every mother of a syphilitic child has either a latent or active infection,

[9] E. Hoffmann, Aetiologie der Syphilis, Springer, 1906, p. 42. The importance of spirochetes in the mother and fetus as well as in the fetal membranes is emphasized here.

and that she is the carrier of the infection. Statistics which support this are so frequently published and cited in texts that I need not discuss them here.

In support of the theory of paternal syphilis, which formerly Kassowitz, A. Fournier, etc., and even today Finger, Hochsinger,[10] Fischl, Almkvist, Mutzer, and others would not renounce, are a few observations which are regarded by critical clinicians only as rare accidents. Thus, families are described in which a syphilitic husband has been the father of a syphilitic child by a supposedly healthy wife, while she has later given birth to a normal child by a healthy husband, and all serologic examinations of the mother and child (spinal fluid, roentgen ray evidence?) have remained consistently negative. One such observation was published in 1929 by J. Almkvist, the well-known Swedish syphilographer. This was translated into French by Péhu.

Nov. 4, 1914, a mother gave birth to an infant weighing 2,950 gm. who had a syphilitic papular eruption and positive Wassermann reaction. Examination of the mother did not reveal any reason for supposing the existence of syphilis, either clinically or serologically. This woman has been serologically examined 36 times in the past 14 years, always with negative results. June 29, 1935, about 10½ years after the birth of the syphilitic child, she married another husband and was delivered of a child weighing 3,920 gm., completely healthy and showing no symptoms of syphilis. This infant and his mother have been followed by Almkvist; neither has presented clinically or serologically any evidence of syphilis. Thus this physician concludes that the syphilis of the first infant was of paternal origin.

The above case shows more than ten years' interval between the births of the syphilitic and the healthy infant. During such a long period the transmissibility of syphilis usually disappears spontaneously, thus making possible the formulation of the "laws of marriage" of the older clinicians. The birth of a healthy infant is easily explained by the long lapse of time and the fact that the mother probably had a previous latent or manifest syphilis, perhaps healing later spontaneously. Negative serologic reactions do at times occur in syphilis of long duration. Significant conclusion can obviously not be made on the basis of one or two rare cases.

This is still more true in cases in which treatment of the father alone has led to the birth of a normal child after or between the birth of other syphilitic children. Today, such observations must be regarded as coincidences, because formerly treatment consisted only of mercurials, which could influence the transmission of syphilis but slightly, as compared with salvarsan.

Through similar clinical observations, the opinion became established that the sperm of syphilitic men commonly contained and transmitted the germ of the disease. However, since the size of the spirochete in comparison with the sperm head has become known, this theory has had

[10] In Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten, No. 15, the old doctrine is presented by one well versed in this theory.

to be abandoned. The partisans of paternal transmission now consider a "granular virus form" to account for the infection of the ovum. That is also not justifiable, in spite of the intercession of Levaditi, Hochsinger, Meirowsky, and others.[11]

Further, through experiments on apes and rabbits, the "infectiousness of the sperm" of syphilitic men has been proved, and it cannot be denied that, in contrast to reported negative results (A. Neisser, E. Hoffmann and others), at times positive results ensue (Finger and Landsteiner, Uhlenhuth and Mülzer and others). These experiments cannot be of great value because, if the sperm flow contains many spirochetes, the mother will be infected by such a contagious disease before the ovum, which in early development is protected so well by Nature by virtue of its membranes and living metabolic processes.

All clinical observations support the fact that syphilis is usually transmitted by spirochetes occurring in erosions, etc., of the skin or mucous membranes, while it has not been proved that the sperm alone is infectious in men free from such lesions. During the secondary stage, men infect their wives by means of spirochetes transmitted from erosions, papules, and mucous membranes. Spirochetes frequently occur in the urethra, and I believe them responsible for the occasional infectious nature of the sperm flow.[12] Nothing is definitely known about the spirochete content of spermatic fluid in late syphilis. However, I know of one significant fact bearing on this matter. Physicians who have acquired syphilis in the course of their professional duties (usually primary lesions of the fingers) and, in spite of a roseola, have remained free of genital lesions, do not often infect their wives, even when continuing marital relations during the course of the secondary period, when their infection was still undiagnosed. This observation, which I have occasionally made in physicians and also in nurses and laymen, is evidence against the virus content of the spermatic fluid, even during late primary and early secondary stages; this fact is important because of many repeated negative findings. So far as I know, infection of rabbits by repeated injections of naturally obtained spermatic fluid of an infected buck has not been successful.

Finally, the so-called exceptions of Colle's law formerly played an important rôle. They occurred very rarely, and not once were they described by reputable clinicians of wide experience. The appearance of an apparent primary (pseudoprimary lesion) on the nipple of the mother of a syphilitic child was considered a new infection, while today

[11]On the basis of implantation experiments using the method described by Schaudinn, v. Prowazek, and E. Hoffmann, the rolled-up forms (formes en boucle et en pelote) were recently described by Levaditi, Schoen, and Vaisman as a stage of development of the *Spirocheta pallida* (Zentralbl. f. Haut- u. Geschlechtskr: 52, 249).

[12]Czerny and other pediatricians emphasize the fact that in foundling asylums (e.g., Prague) the contagiousness of congenital syphilis is not great and transmission is rare. As the virulence of protozoa is enhanced by characteristic passage of insects, a similar augmentation of the virulence of *Spirocheta pallida* may be possible in weeping papules, erosions, etc. (under anaerobic conditions) which would be of importance in contact infection and may explain the greater frequency of genital lesions compared with extragenital infections.

we know that only a reinduration (superinfection) can occur on a latent syphilitic.[13] Such exceptions to Colle's law are no longer heard. Our greater knowledge of symptom-free reinfection and superinfection, obtained from experimental syphilis, has aided much in the explanation of this fact.

The theory of paternal transmission had progressed far, as shown by the theory of "choc en retour," formulated by the great Ricord. Péhu interpreted this as an indirect infection of the mother by the sperm-infected child, as well as infection by the father, and regarded this theory with scepticism. To us, this theory must appear exaggerated and erroneous; today it is considered only a curiosity.

Here may also be mentioned the theory of syphilis by conception (syphilis conceptionelle précoce), which assumes an especially malignant form of the disease when conception and infection occur simultaneously. Even in a definite postconceptional infection of a mother who was previously healthy at the time of conception, adherents of the theory of paternal transmission have regarded the infection as being carried from the sperm to the ovum, with subsequent infection of the mother through "choc en retour."

As well-known clinicians still cling to these erroneous views, the facts which contradict "paternal transmission of congenital syphilis" will be clearly presented once again. First of all, the records of very rare, doubtful cases are no longer tenable in the face of modern knowledge, even though occasionally they appear significant. We know today that syphilis is so contagious that were a syphilitic man to transmit spirochetes by his sperm to a woman, he would first infect her and not the ovum alone. Spirochetal infection of the ovum and not the more accessible mother is therefore to be regarded as improbable, if not impossible. Also it is hardly conceivable that a holoblastic ovum,[14] such as the human, would continue to develop if it were syphilized, because even later, in the fetus, immunity is lacking or is so slight that with early diaplacental infection spirochetes overwhelm it and can cause its death. A matter of decisive importance is the fact that spirochetes have never been found in the fetus of syphilitic mothers nor in the fetal portion of the membranes before the fifth month of pregnancy. Rare exceptions toward the end of the fourth month, such as the fetus described by Gräfenberg and others, are not definite, while others carefully described by Oluf Thomson, Paul Schneider, etc., showed nothing. If a germinative infection occurred, spirochetes would be expected to develop in such numbers in the fetus during the first half of pregnancy, that they could be demonstrated without difficulty in the first months of pregnancy.

[13] E. Hoffmann, Dermat. Ztschr. 12: 491, 1905.

[14] As interesting as they may be, the observations made by Levaditi on mereoblastic ova (spirochete of chickens) have no importance for human pathology; similarly, the experiments with pébrine (a disease of silkworms) have no bearing on the question.

How enormously spirochetes can multiply in very young animals, e.g., chickens, is shown by the inoculation of *Spirocheta gallinarum* into newly hatched chicks; the research done in my laboratory by Kroó[15] is also significant in regard to this question. The germinative—that is, the oogenic as well as the spermatogenic—transmission of syphilis may therefore be regarded today as entirely unproved. Attempts to preserve this doctrine by older and even by more recent clinical observations are of minor importance when opposed by the great mass of available research.

B. *Diaplacental Infection.*—As has been emphasized by G. Herxheimer in his excellent article (Wiesbaden, 1928) and in my papers (Hamburg, 1928, and Koenigsberg, 1929), only the diaplacental route of infection remains, and Matzenauer's statement, "Without a syphilitic mother there can be no syphilitic child," may today be considered entirely valid. Matzenauer's theory, which Rietschel and I have long supported (Handb. d. Hautkr. 19), that transmission first occurs by way of the placenta and umbilical cord during the second half of pregnancy, most frequently in the sixth and seventh months, can be amplified on the basis of new research, confirmed by Klaften in conjunction with O. Thomson, P. Schneider, and others. Thus, the earlier view that syphilis was the result of a germinative infection has lost favor, this chronic infection following the rule of transmission of the etiologic agents from the mother to the child.

The transmission of *Spirocheta pallida* occurs regularly from the infected mother to the fetus; in general, it occurs more intensively and more frequently if the mother's infection is fresh and severe. In cases of severe, untreated infection, this results in the early expulsion of a diseased and dead fetus. In the course of time, the intensity of the syphilis gradually diminishes, even without specific treatment, and children are born at term, manifestly infected or apparently uninfected, the latter sooner or later showing signs of syphilis. The birth of a completely healthy infant can occur between stillbirths or infected children. The "spontaneous gradual diminution of the intensity of syphilitic transmission," according to Kasowitz' rule, which in general holds good, is thereby broken. The cause of this lapse lies, first, in the fluctuation of intensity of the mother's infection and the number of virulent organisms which enter the blood stream, and, further, in the extent of localized infection within the mother's placenta, conditioned by the organisms in the blood. This irregularity of fetal infection is well illustrated by the fact that twins are not necessarily equally severely infected; indeed, one may be healthy and the other syphilitic. One such occurrence was reported in uniovular twins and, I believe, can be explained by the localization of foci of infection in the placenta and umbilical cord.

[15]The chicks do not react clinically to the immense multiplication of spirochetes. Hoffmann, Aetologie der Syphilis, Springer, 1906, 42.

It has recently become recognized that habitual abortion during the first months of pregnancy is not always due to syphilis but to the same causes as in nonsyphilitic women, while stillbirths and premature births occurring during the second half of pregnancy (fifth and sixth months on) are suggestive of syphilis. However, in spite of this, in actual practice, abortions should always be investigated for the presence of syphilis.

The participation of the obstetrician in the investigation of and battle against congenital syphilis has become very important. In addition to the course of the pregnancy, the pathologic-anatomic changes which are found in the placenta and umbilical cord are of great significance and can frequently be shown to be specific by the presence of spirochetes. The placentas of syphilitic fetuses and of syphilitic children are usually abnormally large and heavy in proportion to the body weight of the child. I have termed this proportion of placental to infant or fetal weight the placental quotient. At the end of gravidity, it is usually 1:6 for the normal, 1:5 for the syphilitic, and even 1:4 and more in premature births, thus at least arousing suspicion of syphilis.[16] The placenta also shows pathologic changes which consist of proliferation of capillary endothelium and stroma cells, diminution of intervillous spaces, the so-called abscesses in the villae, and vascular changes which are manifested as an obliterating endovasculitis, which Kaufmann found in 16 per cent of cases. Anemic infarcts, which Virchow first thought to be gummas, and infiltrates containing giant cells occur especially in the maternal portion of the placenta. Frequently the umbilical cord likewise shows perivasculitis, mesovasculitis, and endovasculitis with small cell infiltration, which is more pronounced in the adventitia and media at both ends of the cord. The focal arrangement stands out in a characteristic manner in and around the umbilical vein, which is frequently involved.

All these changes, in themselves not characteristic of syphilis, demand consideration, and further studies, such as dark-field examination and silver stains of sections, should be carried out in establishing proof of the etiologic agent. Spirochetes are frequently present in the walls of the umbilical vessels and can be found at times in scrapings of the intima and media of the umbilical vein which is generally involved severely. In the placenta, spirochetes are often as numerous in the fetal as in the maternal portion, although they invade primarily from the latter portion; this may be due to the influence of immunity developed in the maternal organism, as well as to its high oxygen content.[17] The transmission of the anaerobic spirochetes into the fetal portion does not occur before the fifth month of gestation. Probably an occasional spirochete suffices to infect the fetus owing to an almost complete absence of immunity in

[16] E. Hoffmann: Dermat. Ztschr. 54, 369 and 57, 145.

[17] The small number of *Spirocheta pallida* in the oxygen-rich placenta and in the blood, as well as their situation in the tissue, led me in 1905 to infer that the spirochete was anaerobic, a fact which Schaudinn at first doubted.

the latter, the severity of the infection being proportional to the invading masses of microbes (involvement of the vessel walls). This invasion can enter directly into the blood stream or, in addition, can occur through the lymphatic passages,[18] in which case, as I stated in 1928, a sort of primary complex can develop in the fetal placenta and in the umbilical cord up to the liver vessels. Thus, occasionally, a specific phlebitis can appear in the infected liver (Beitske). By animal experimentation (rabbits), healthy placentas have been penetrated by the *Spirocheta pallida* and similar spirochetes (Philipp and others); this is not true for the larger parasites, such as trypanosomes. These tedious experiments, however, do not have any great significance when applied to human pathology. My hope that animals with longer periods of gestation (e.g., llamas) could be used in these experiments has thus far remained unfulfilled.

Transmission of *Spirocheta pallida* can occur until the end of pregnancy. The number of transmitted germs may depend on the age and intensity of the maternal infection and on the number of spirochetes still motile and present in the blood stream, as well as on the extent of localized infection in the maternal placenta. Thus, the protecting barriers to the fetal portion of the placenta may break down in the case of a maternal infection acquired shortly before or during pregnancy, with an ensuing high spirochetal content of the maternal blood resulting in numerous placental foci. The earlier this fetal invasion occurs (fifth to sixth months) with consequent greater invasion of the fetal blood, lymphatic and tissue routes, the more intense will be the infection of the fetus which is not yet protected by any immunity. Because of the absence of immune processes, an unchecked increase of parasites may occur in the fetus and thereby cause its death. Involvement of vessels with narrowing of their lumen, as observed in the syphilitic placenta, results in deficient nourishment. Transmission of spirochetes may occur long after the original maternal infection, due to the fact that acquired syphilis may run a course of exacerbations and, when untreated, recurrences are possible during many years.

On the other hand, even with a fresh syphilis of the mother which has not been specifically treated, transmission may occur late or, more rarely, not at all. Thus may apparently normal or really normal children be born. The fact that the former frequently show evidences of syphilis four to eight weeks or within the first four years after birth has given rise to the opinion that transmission of spirochetes first occurs shortly before birth or—what may be rare—during it, due to loosening of the placenta (H. Rietschel).[19] This type of congenital syphilis, becoming

[18] H. Rietschel first suggested this possibility in 1913.

[19] Late transmissions are frequently reported, as for example, I. Levin considered an infection as occurring fourteen days before birth on the basis of the appearance of a primary lesion on the mother ten days later (ten days postcoitus and four days prepartum!) and the infant having Coryza syphilitica twenty-five days after birth, and an exanthema and weakly positive serologic reaction forty-four days after birth. (Zentralbl. f. Haut- u. Geschlechtskr. 51, 589).

recognizable some weeks or months after birth, could be designated as syphilis postnatalis, or as syphilis congenita, innata, and connatalis.

All degrees of severity of infection are evident, ranging from a macerated fetus and severe visceral and bone syphilis of affected children (syphilis innata) to the apparently healthy infant (syphilis connatalis or postnatalis asymptomatica). These types are explained by the manner and severity and, above all, by the time of invasion and numbers of spirochetes invading through the maternal placenta whose protective function eventually fails to a greater or lesser degree. It is not clear as to the extent to which antigenic substances traversing the placenta play a part in mitigating the infant infection.

It should be further emphasized here that the severity as well as the frequency of fetal syphilis has significantly become reduced during the last decades. This fact is cited in the new Handbuch and in many individual articles and is ascribed to salvarsan therapy during pregnancy, a therapy which has also aided in a reduction of syphilis in general. Before I discuss this further, some questions of acquired infant syphilis must be considered.

C. *Binary and Acquired Syphilis.*—Pasini questioned whether there was a sharp distinction between congenital and acquired syphilis of the newborn, and I explained the possibility of mixed infections, i.e., a binary congenital syphilis.

All infections occurring by hematogenous or lymphogenous routes and not exogenous (with or without a primary lesion) are considered as syphilis congenita; infection takes place through the umbilical cord, which may present a phlebitis. Rare cases of deep or superficial, chancre-like, umbilical ulcers, which, according to Hutinel, L. F. Meyer and others, appear about three weeks after birth, have been regarded as lymphatic infections occurring through the umbilical cord. Similar forms of infection, rarely noted, approach acquired infant syphilis in appearance and are difficult to differentiate from an exogenous infection of the umbilicus occurring during or shortly after birth.

As I have pointed out in previous articles, a double infection is possible, giving rise to syphilis congenita binaria, only one case of which, reported by Schilling and V. Hoffmann,[20] was I able to accept as definite. This mixed form can occur when a child, infected before birth by diaplacental transmission of spirochetes from the mother, receives a second or superinfection of spirochetes through the skin during the passage through a birth canal containing infectious papules or erosions. This superinfection can be manifested by a primary on the head, or more rarely elsewhere, but may occur asymptomatically. The spirochetes, derived from the same source, namely, the still infectious mother, reach the child by two different routes: most important, before birth through the umbilical cord, and then later through the skin at time of delivery.

[20]Jadassohn's Handb. d. Haut- u. Geschlechtskr. 17/3, 168.

Naturally there remains the possibility that an exogenous infection after birth can originate from the same or from another source of infection (wet nurses, nurses, etc.).

Such infections "en passage" are very rare, A. Fournier stating that he had never seen one. In my article on binary syphilis of nursing infants,[21] I referred to ten cases of proved primaries on the heads of nursing infants and believe that these are frequently overlooked because they are often insignificant and the regional lymphadenitis may be minimal. Consequently, the question whether there is a sharp borderline between acquired and congenital syphilis in infants deserves more consideration, and our best efforts must be given to the study of the possibility of superinfection and to careful investigation of binary syphilis of the newborn. Thus might be explained the appearance of keratitis profunda, etc., following what would appear to be an acquired syphilis in infancy.

Tarnowsky described binary syphilis of older individuals with signs of late congenital syphilis, which should be differentiated from binary syphilis of nursing infants and should be considered as a reinfection or superinfection of an older congenital syphilitic, in whom the skin immunity, with or without specific therapy, has decreased to such an extent as to permit a true primary or a pseudoprimary lesion. The possibility of a symptom-free superinfection should always be considered; also, reinfection without an obvious primary lesion may prove to be more important than was formerly thought in doubtful cases, causing late recurrences after an apparently successful cure of adults and of children.

Most pediatricians regard acquired infant syphilis as rare and proportionately unimportant; as Czerny emphasizes, it usually runs a less severe course than in adults.[22] Unfortunately erroneous views prevail which have been represented by illustrations and descriptions in well-known textbooks and thereby have been uncritically disseminated. Pictures of older children of six years or more with alopecia microareolaris, which is a typical early manifestation of an acquired syphilis and is encountered in adults only in the first year, are presented as "late recurrences of congenital syphilis" (Ledermann in Jadassohn's Handbuch,[23] E. Müller in Pfaundler's Handbuch, Feer,[24] etc.). Also, leucoderma and vegetating condylomas occurring in well-nourished infants and older children are indicative of an acquired (or binary) and not a congenital infection.[25] The primary lesion may frequently be concealed, for example, on the tonsil, and is easily overlooked.

[21]Deutsche med. Wchnschr. 1929, 1289; Schweiz. med. Wchnschr. 1929, 1213; and Dermat Ztschr. 54 (1928), 369 and 57 (1930), 150.

[22]Other authors, such as Rietschel, do not share this view.

[23]Jadassohn's Handbuch, 19, 73.

[24]Lehrb., 9, Edition 1926, 723 (Condyloma).

[25]Experienced pediatricians, such as H. Rietschel, believe that such condylomata are never observed as an original lesion, but rather as a recurrent lesion after the first year of life, and then only rarely.

D. *Frequency of Congenital Syphilis.*—The occurrence of congenital syphilis has been significantly reduced. E. Müller, Klaften, Péhu, Lomholt, and others have made statistical studies and have attributed this reduction to successful treatment with salvarsan preparations, which has also caused a decrease in the formerly marked polymorphism and severity of congenital syphilis. The statistics presented by authors in different countries vary considerably.

In many countries (e.g., Brazil, Russia, etc.) they are higher than in Germany. Years ago Buschke estimated the number of stillbirths in Germany as 20 per 25,000, and Baisch as 20 per 10,000. According to the German census of 1927, there were about 7,500 living children with congenital syphilis. In the children's clinics, from 2 to 4 per cent of infants were found to be syphilitic. In England and France these figures are higher and reach 10 per cent, and in France and its colonies even 20 per cent and more. To be sure, doubtful cases (hereditary distrophies, etc.) have been included. The number of premature and stillbirths due to syphilis was given as 50 to 90 per cent by Weber and Reischig; Reischig found 81.1 per cent and Gräfenberg found 92 per cent of the stillborn to be macerated. The mortality of the infants born alive was high; Noeggerath showed that it was from 50 to 67 per cent in hospitals, from 24 to 35 per cent in nursing homes, and from 15 to 19 per cent in out-patients (those less severely involved). The greatest number of these infants died in the first year, especially during the first four months. The devastating effect which syphilis exercises on progeny is shown by Hochsinger's great work; he followed 266 pregnancies in 67 families and found that 46.6 per cent of the pregnancies resulted in premature stillbirths, 28.6 per cent in infant mortality within the first year, while only 24.8 per cent of the infants remained alive. Gammeltoft found only 7 (3.5 per cent) healthy children among 201 children of untreated syphilitic mothers. Hata could prove only 5 healthy children over five years of age in 100 syphilitic marriages.

These few but startling figures suffice to show the devastating effect of syphilis on progeny before the introduction of modern therapeutic methods.

Another arresting fact is the percentage of pregnant women who have syphilis. This was investigated by Blumenthal and myself in 1908[26] and also by others since then.

The figures obtained ranged from 8 to 10 per cent, and in Halle, reached even up to 20 per cent; they fell to 5 to 6 per cent and are now still lower (4 per cent). On the basis of compilation, Klaften estimated the average frequency of syphilis among pregnant women in Europe as about 4.5 per cent to 5.5 per cent; in America, 6.8 per cent. These figures have been greatly reduced wherever there is satisfactory treatment. In 1926-27 Philipp and Richter[27] found 65 syphilitic children among 5,028 births in the Berliner Frauenklinik, which is scarcely 1.3 per cent. In 1931-32, there were only 22 syphilitic children among 4,073 births, or only 0.5 per cent. The number of macerated syphilitic stillborn decreased during this period from 42 in 1926-27 to 7 in 1931-32, which fact is still more striking.

In Denmark, where the statistics are exceptionally accurate, due to an excellent central card index system, the yearly census of congenital syph-

[26] Dermat. Ztschr. 15, 23 and 17, 1 and 82.
[27] München. med. Wchnschr. 1933, 1540.

ilis has dropped from 280 in 1920 to 29 in 1931 (Lomholt[28]). I understand that in Vienna, in spite of weak doses of salvarsan (only 0.3 gm. of neosalvarsan per week) used in the treatment of pregnant syphilitic women, there is a disappearance of the macerated fetus, as well as a significant reduction of congenital syphilis, a fact noted by different authors. The statistics of the northern countries are similar to the Danish, thus demonstrating the success of treatment.

There is much in the literature about the transmission of syphilis to the second generation (termed by many, the third generation).

That an insufficiently treated or an untreated woman with congenital syphilis can exceptionally transmit syphilis to her child is admitted by clinicians, and a compilation made by Feige under my direction and newer studies show that a few cases may meet the rigid requirements of Fournier, Finger, and others. That transmission is also possible to the third generation (also termed the fourth) is asserted but has not been ascertained. These questions cannot be further discussed here because they have no bearing on the problem which interests us and, due to our modern therapeutic knowledge, are no longer as important as formerly.[29]

E. *Doubtful Infections (Malformations, Hereditary Dystrophies, and Syphilis Larvée).*—Finally there is another question, much discussed in the French literature, as to whether syphilis can engender monstrosities, malformations and dystrophies. This question has been exhaustively treated and criticized by Péhu. There is also the question as to whether a syphilitic toxin is capable of impairing the germ plasm, thus producing a blastophthoria. In my articles (1928-29), I opposed the idea that injury to the germ plasm can result without a diaplacental transmission of *Spirocheta pallida.* It also appears to me that this stand, already supported by Husler and others, is justified and I believe that it is worthy of being reemphasized. Whoever considers such a vague theory[30] must admit that syphilis by its influence on the germ plasm would have greatly damaged the human race during the last hundred years in the countries in which it is widespread. We know, however, that children of otherwise healthy syphilitic parents who are no longer infectious can be entirely normal. Indeed it is remarkable that extremely good-looking and healthy children have been born into otherwise unblemished families of old syphilities and paralytics, when marriage occurred after loss of transmissibility of the syphilis. The regularity with which healthy children are born, after intensive prenatal therapy with modern preparations (neosalvarsan, bismuth), supports this view.

The statements about the occurrence of monstrosities, malformations, and dystrophies are likewise derived from the experience and imagination of older clinicians and are vague and far-reaching and in need of

[28]Dermat. Wchnschr. 100, 173.

[29]Schönfeld: Dermat. Ztschr. 72: 119.

[30]Fr. v. Müller formerly supported this theory on the basis of several observations in syphilitic families, which, however, can be explained otherwise.

revision. When syphilis was still more rife, and in regions where it was widespread (Paris, Morocco, etc.), even great clinicians ascribed unrelated conditions to syphilis. Thus Lewin once believed that maculae caeruleae, which are due to pediculosis, were a special type of syphilitic exanthemas, while in France, vitiligo, alopecia areata, the tubercle of Carabelli, and many other conditions were ascribed to syphilis. The famous A. Fournier, who first included tabes, general paralysis and aneurysms as syphilitic manifestations, also ascribed numerous dystrophies of the teeth and other organs to syphilis, thus making, in addition to his observations of lasting value, unfortunate statements which have proved to be completely fallacious. It is still held that tuberculosis, rachitis, and other ills can occur on the basis of a congenital syphilis; a lamentable interpretation which, similar to the error of the great Hunter, has resulted in serious consequences. Recently French authors, such as Hutinel and others, considered such disturbances as residues of persisting infections of the infant and due to a specific involvement of the endocrine glands. Schneider, in his article in 1928, collected and reviewed the pathologic changes and spirochetal findings in these glands; also E. Müller, Péhu, and Kerl mentioned them. Interesting as this problem may be, I cannot discuss it further because of my limited personal experience. J. Darier in his excellent text (1928) included, in addition to "hérédosyphilis virulente," the "hérédodistrophies"; he characterized them as "troubles of physical development, a disposition to malformations such as an alcoholic or tuberculous father might cause," and said that these hereditary dystrophies can occur with or without a congenital syphilitic infection.

It is a recognized fact that certain severe dystrophic manifestations, such as the cicatrices of Parrot and other stigmas of the teeth, bones, sensory organs, etc., are evidence of congenital syphilis. These are explained by a lower degree of spirochetogenic involvement. If monstrosities, malformations, and dystrophies in syphilitic families occur without diaplacental transmission of spirochetes, they cannot be ascribed to syphilis. In this respect, it seems to me that the viewpoint accepted in Germany (Rietschel, E. Hoffmann, and others) is critical and correct. Whoever maintains a relation between syphilis and dystrophies must demonstrate the cause and prove the presence of the etiologic agent itself or its acknowledged consequences (inoculation, spinal fluid, serologic reactions, etc.). Because syphilis is extremely polymorphic in its manifestations and because of the possibility of simulation of other diseases (it has been termed the "great imitator"), the opinions of the French school should not be shared when it comes to diagnosis and delimitation. Instead, the rule, "Consider syphilis," should always be followed. If such vague and insufficiently proved theories, which still persist in France, of the "dystrophic sequences of syphilitic toxins" and the influence of hereditary factors were seriously admitted, the progress made

by the research of the last three decades would be lost. The theory of "syphilis larvée" and Péhu's fourteen subdivisions,[31] which include all the dystrophies and malformations as well as monstrosities in the various organs, would permit the possibility of a syphilitic origin for all human pathology, as Péhu himself admitted.

Rietschel devoted an article (Med. Klinik, 1931) to a critical résumé of these questionable doctrines and cited reasons why such a position is uncritical and untenable from a clinical standpoint.

Today it is a requisite of medical science to establish more stringent diagnostic criteria for the hereditary dystrophies and to eradicate exaggerated and uncritical theories. Only where the *Spirocheta pallida* can be found, or definite manifestations of it can be proved, are dystrophic processes to be considered as specific. All other dystrophies and malformations should be investigated on the basis of familial inferiority (mental or otherwise) or of true toxic causes (alcohol?) and, even if they are present in the same patient along with congenital syphilis, they should not necessarily be ascribed to the syphilis.

Before a syphilitic toxic influence from the mother to the ovum or fetus can be established, experimental proof on pregnant animals (rabbits) must be obtained. This could be done by repeated injections, before and after coitus, of macerated organs rich in spirochetes—after heating to the death point of the spirochetes. Similar experiments could be carried out with alcohol and other substances having a possible influence on heredity. The assertion made by prominent clinicians—I mention here only R. Sabouraud, the world famous mycologist—that the abnormal tubercle of Carabelli be regarded as a sign of congenital syphilis shows how misleading purely clinical observations and statistics can be. In countries where syphilis was, or still is, widespread, it is often present along with other diseases, as well as tuberculosis, and may be so masked by them that false conclusions are understandable. The difficulty of correcting such errors is repeatedly shown in the history of medicine, and not infrequently even the most outstanding clinicians and pathologists (A. Fournier, E. Finger, R. Virchow) have at times held on to opinions in the realm of the chronic infectious diseases (syphilis, tuberculosis), which were later proved erroneous. In the French literature the opinion is held that tuberculosis can be considered only when it can be proved to be the result of infection with Koch's bacillus. When the same requirements are accepted for the *Spirocheta pallida*, a lengthy and violent controversy will end abruptly.

[31]According to Péhu, hérédosyphilis larvée can be manifested by : (1) developmental disturbances, (2) nutritional disturbances, (3) endocrine disturbances, (4) osteoarticular manifestations, (5) nervous involvement, (6) digestive syndromes, (7) hepatic syndromes, (8) respiratory syndromes, (9) cardiovascular affections, (10) renal syndromes, (11) cutaneous manifestations, (12) blood changes, (13) involvement of the lymphatic system, (14) congenital malformations.

III. PATHOLOGIC ANATOMY

Only a few important points of general pathology will be presented here, the subject having been thoroughly discussed by G. Herxheimer and P. Schneider in their Wiesbaden publications.

A. *General Considerations.*—Shortly after their transmission to the fetus, during the fifth month of pregnancy or later, the spirochetes multiply in the fetal organism without producing a reaction and disseminate through the fetus in immense numbers. To a much less degree, this is also true for acquired syphilis, where a severe, occult proliferation is present, not only in the early incubation period before the appearance of the primary lesion, but also in the secondary period in the roseolas and papules, etc., which are hematogenous in origin. As I have emphasized for thirty years, tissue reactions, not only the inflammations that are recognizable microscopically, but also the clinical manifestations, occur considerably after the invasion of the spirochetes. We know today that an asymptomatic infection[32] may persist which merits attention in connection with gravid and congenital syphilis. As I have explained, the limited numbers of *Spirocheta pallida* in the blood and in the maternal placenta are due to the high oxygen content which destroys the anaerobic spirochetes; but under anaerobic conditions in the macerated fetus, an unlimited multiplication of spirochetes can take place. The opinion that this unchecked proliferation occurs after death has only been partially ascertained; as soon as there is a lack of oxygen due to edema and constriction of the lumena of the placental vessels, favorable cultural conditions prevail in the fetus, and, owing to lack of immunity, an unlimited increase of the microbes takes place. Expulsion of the fetus occurs several weeks after its death, thus affording in its oxygen-free tissue a great opportunity for unlimited multiplication of spirochetes. This finally results in partial decomposition of the fetus as a consequence of maceration following fermentative processes. G. Herxheimer has justly emphasized the anergy present in the young fetus of this type; and transmission of protecting immunity from the mother through the diseased placenta cannot really be considered when such severe endovasculitis is present.

The histological pathology of congenital syphilis is similar to that of acquired and experimental animal syphilis. It is distinguished by an inflammation of the blood vessels which may involve the walls of the veins, arteries and lymph vessels, even the capillaries and lymph spaces. The *Spirocheta pallida*, as I have emphasized since 1905, is a lymphatic and connective tissue parasite which behaves differently than the blood spirochetes. In spite of my repeated references to this fact, this difference is underestimated, as is the importance of the anaerobic tendencies of the *Spirocheta pallida*.

[32] Experimentally proved by Kolle and others in mice and rabbits.

It does not seem, therefore, justifiable to speak of a septicemia in congenital or even acquired syphilis (septicémie syphilitique primo-secondaire[33]). Proof of the presence of *Spirocheta pallida* in the oxygenated blood stream is very difficult in the living child, even in the most severe forms of congenital syphilis.[34] Anaerobic *Spirocheta pallida* do not thrive in the blood but escape from the blood stream as quickly as possible, and are much more frequently found in the endothelium and perithelium of the blood capillaries and lymph spaces, and in the vessel walls, often surrounding the vasa vasorum. The endothelium becomes irritated, with resultant edema, proliferation, and hypertrophy; this has been determined experimentally in my laboratory during the primary incubation period of syphilis in rabbits, by G. Armuzzi, a student of mine for many years, who carried out my suggestions carefully. In the perivascular lymph spaces and in blood and venous thrombi, which have a low oxygen content, occasional or numerous *Spirocheta pallida* can be found, and also a few in regional lymph glands as early as twenty-four hours after infection, while they have been found in the spleen forty-two hours after infection by silver staining of sections (my student, Emil Zurhelle).

The true cytotropic reaction, which appears in addition to the endovasculitis, mesovasculitis, and perivasculitis, follows as a more or less allergic reaction, is related to vascular endothelium, and is considered by Aschoff as a defense mechanism of the reticuloendothelial system. This reaction is not uniform but appears in isolated islands, so that free zones always remain between the foci of perivascular infiltration. This focal distribution is also characteristic of the nests of spirochetes and is reflected in the histologic picture. In addition, there appears a unmistakable sclerotic change of the collagenous tissue, which in rabbits is accompanied by a myxomatous exudation, and in man by lymphedema and a less noticeable degeneration of the connective tissue.

The characteristic cell picture of syphilis does not consist of a pure plasmoma, as Unna assumed. Cell counts of tissue from chancres and later syphilomas, which have been made by various French authors (Nanta, Laurentier, and others), show from 35 to 63 per cent small lymphocytes, about 10 per cent large lymphocytes, and 10 per cent each of mononuclears and plasma cells; however the number of plasma cells is usually considerably greater, according to my experience and that of other German pathologists and syphilologists. In congenital syphilis, plasma cells are at first absent and later are more rarely found than in acquired syphilis.

French authors further assume a proliferation and even a wandering of the endothelium. They emphasize that giant cells, which are more

[33]Sézary: Traité de la Syphilis (Jeanselme) III, 65.

[34]I sometimes found them in dark-field examination in severely involved nursing infants (Berl. klin. Wchnschr., 351, 1907).

frequent in the many lupoid forms of syphilis and even involve vessel walls, are of endothelial origin. I frequently have seen convincing examples of this in small vessels (veins) which are being destroyed by endovasculitis.

B. *Bone Involvement.*—In the dearth of other symptoms, the bony involvements have become very important in the detection of fetal and early forms of congenital syphilis, not only because of their spirochetal content, but because they are recognizable roentgenologically. The most important form is the classical Wegnerian involvement of the epiphyseal borders of the long bones (femur, tibia, etc.) which is also manifested in the cartilaginous borders of the ribs and elsewhere. These changes can occur from the fifth fetal month onward. The great frequency of bone involvement and its significance in Parrot's disease (a pseudoparalysis due to epiphyseal separation) give it a special value for syphilologists, pediatricians, obstetricians, and pathologists. Next in importance to osteochondritis is periostitis syphilitica; this form may begin in fetal life but usually appears somewhat later. In addition, German authors mention the osteomyelitis fibrosa rarefícans of Pick, and Péhu also cites a productive hyperplastic form. A type characterized by transverse shadow bands (Klaften) has recently been reported which can be recognized roentgenologically and which occurs following prenatal specific therapy in Wegner's disease.

On the basis of thorough researches by O. Thomsen, P. Schneider, L. Pick, M. Péhu, and others, it may be said that spirochetes are present in their classical form in the growth centers of the bones, but not before the fifth month of pregnancy. In the absence of any reaction the spirochete is the only certain indication of a progressive but otherwise latent infection; the stratum of cartilaginous development is its site of predilection, while this form of involvement does not occur in the membranous bones. Osteochondritis regularly occurs symmetrically, is often recognizable by roentgenographic examination before and at birth, and is easily differentiated from rachitis up to the third month. In the course of the first three or four months, the osteochondritis recedes spontaneously and disappears as a generalized symmetrical involvement, while other forms become more pronounced (periostitis, localized lesions, etc.).

Thus, osteochrondritis syphilitica is not, as its name signifies, an inflammatory process from the beginning, but is a characteristic alteration at the border of the developmental zone between the diaphysis and epiphysis of the long bones, ribs, etc., the ossification of which is disturbed in the cartilaginous stratum. The normal epiphyseal borders, which ordinarily appear as a regular narrow white line, become an irregular, zigzagged, yellowish white streak seldom more than 4 mm. in width. At a further stage in development, a striking zone of yellowish tissue arises which projects in tonguelike forms of different lengths into the epiphysis. Under the influence of the *Spirocheta pallida*, which

causes little or no reaction in the fetal organism, bone formation is disturbed and greatly delayed, while the cartilaginous columns develop in the usual manner. Gratelike arrangements of calcified cartilage appear in the widened zones of calcification, the so-called "Kalkgitter" or calcified grate, between which normal cartilage remains. With severe degrees of involvement, in the course of time, a band of granulation tissue, which arises from the connective tissue of the young bone marrow, is interpolated between the bones and the zone of calcification. This results in a spongy connection between the bony diaphysis and the cartilaginous epiphysis, and at times in a complete epiphyseal separation due to a fracture in the region of the "Kalkgitter" or at the border between the zone of calcification and uncalcified cartilage, thus producing the clinical picture of Parrot's pseudoparalysis. This anatomic process is usually more frequently and more marked in the lower extremities at the distal ends of the femur and tibia, while the hip and proximal ends of the tibia and humerus, as well as the radius and ulna, are less frequently and less severely involved. The ribs and smaller round bones are also more or less altered, as can be demonstrated roentgenologically (L. Pick and others). Parrot's pseudoparalysis shows a preference for the upper arm, which is easily traumatized. These sequences, which do not always occur in a regular order (Wimberger), demonstrate that primarily the lower extremities and wrists of the newborn merit roentgenographic study (Péhu and others[35]).

The degree of involvement recognizable anatomically as well as roentgenologically has been divided into three stages. In the first stage, the provisional zone of calcification is somewhat broadened. In the second stage, it is 3 or 4 cm. wide and is visibly serrated with granulation tissue projecting into the region of the "Kalkgitter" zone. In the third stage, in addition to the other disturbances named, this granulation tissue has so increased that it results in sponginess and even in epiphyseal separation (pseudoparalysis).

This gradual process, which is very marked in the premature and the newborn, is demonstrable to a less extent by roentgenograms of the fetus in utero. Péhu and Policard believe that at first a clear zone, broader than normal, and near the diaphysis is characteristic of the roentgenogram, and that longitudinal serrations in the "Kalkgitter" zone become visible as dark lines resembling pencil marks. This roentgen evidence is often still more striking because of the presence of double-contoured dark stripes.

Periostitis syphilitica can likewise begin in intrauterine life but occurs less commonly in the first months, becoming marked usually after the third month of life, and assuming more importance in later childhood. This condition is manifested in the long bones and elsewhere and is

[35]Good illustrations are found in L. Pick's article, "Angeborene Knochensyphilis," in the Handb. d. pathol. Anat. (9/1), and in other textbooks, and are therefore not included here.

recognizable roentgenographically, in consequence of its ossification, as a cup-shaped dark line. Periostitis ossificans also appears in the phalanges and skull bones during childhood. Also periostial hyperostoses can be present on the skull in early life; they later produce characteristic stigmas, especially of the tibia (saber shin).

Schneider has called attention to two types of osteochondritis which are not strictly delimited; namely, the passive type with marked spirochetal infiltration of the fetal tissue, and the later active type, in which more and more reactive processes slowly appear with formation of granulation tissue.

C. *Active and Passive Process (Miliary Syphiloma).*—Schneider's division into passive and active processes is basically important for the changes in other organs. Thus, many organs are infiltrated by immense masses of spirochetes without evidence at first of a perivascular or an interstitial inflammation, while later, if the defense mechanism in the last fetal months or at the time of birth develops slowly and thereafter becomes stronger, these reactive processes stand out more prominently. A dense spirochetal infiltration is found, for example, in the suprarenal gland, where the microbes are ordinarily found between the cells. Here, as French authors have pointed out, a marked opposition exists to the ultravirus, which lies within the parenchymal cells or within the nuclei. The difference between an early anergic reaction, then a hypoallergic reaction, and rarely an allergic reaction, is decreased about the time of birth and later becomes still less; then the so-called miliary syphilomas and nodular pseudogummas can occur in addition to an interstitial proliferative inflammation. These pseudogummas were formerly considered to be veritable gummas (R. Virchow and others), but can be differentiated from gummas by their extraordinarily rich spirochetal content. Indeed, the first case of congenital syphilis in which I found *Spirocheta pallida* in the liver, lymph glands, etc. (spring of 1905), was distinguished by such pseudogummas.[36]

Miliary syphilomas, which I have produced experimentally in rabbits,[37] occur as small nodules most frequently in the liver, but also in other organs (bones, etc.) and consist of polymorphic, degenerated, occasionally necrotic cells, and usually contain spirochetal colonies which can be stained by silver methods. Similar in structure are the larger nodules, which resemble gummas more closely; whether a hyperallergic inflammation has played a part in these as in the true gummas appears doubtful in view of their rich spirochetal content. The so-called thymus abscesses of Dubois, as well as the characteristic pneumonia alba, contain large numbers of spirochetes.

[36] Berl. klin. Wchnschr. 1905, 728 and 1022-5.

[37] I found miliary nodules containing giant-cells in the tumorlike, older primaries in the rabbit cornea. (Dermat. Ztschr. 41, 236, Plate II, Fig. 3).

Unfortunately, it is not possible for me to enter further into these interesting pathological changes and their significance. I may, however, refer to articles by G. Herxheimer, P. Schneider[38] and to the new Handbuch.

IV. CLINICAL MANIFESTATIONS

In connection with this general presentation of the pathogenesis and frequency of congenital syphilis, its symptomatology, which is easily found in textbooks, will only be mentioned briefly before I discuss the early diagnosis and treatment. As has already been stated, the severe symptoms, which previously were so frequently encountered by clinicians in their classical forms, have become rarer, and the picture of congenital syphilis has changed much more than that of acquired syphilis, in that it has become essentially more uniform and presents fewer symptoms.

Pathologic changes present in the dead fetus, placenta, and umbilical cord are of interest primarily to the obstetrician and pathologist. Because they have already been discussed, I will only mention that they result in the expulsion of the macerated fetus, or in the premature birth of syphilitic children, who are retarded in their development. A macerated fetus occurs rarely in the fifth, usually in the sixth to seventh, month of pregnancy; the living infants are delivered at this period. As already mentioned, with a young macerated fetus, there is a complete absence of reaction on the part of the tissue in spite of the immense numbers of spirochetes. Foci of spirochetes are present in the cartilaginous borders of the long bones, as well as changes indicative of the osteochondritis of Wegner. The resultant widening and irregularity of the cartilaginous border is diagnostically the most important sign of fetal syphilis. The chemistry of the developmental processes has been considered as an explanation for the fact that the spirochetes settle in these locations, after having previously flooded the liver from the blood stream. According to Schneider and others, the spirochetes occur here in large numbers and also at times, as Bertarelli found, in the osteoplastic centers.[39] Similar residual or inactive foci—also in the periostium, etc.—are of significance in the explanation of persistent positive serologic reactions, or reactions becoming positive upon provocative treatment; if the foci are small and walled off, a continuing negative serologic reaction can occur, though this is rare.

A. *Severe Forms of Involvement.*—Osteochondritis is often accompanied by a severe nutritional disturbance, which is evidenced by the senile, atrophic appearance of the fetus and of the child. The color of the skin is a peculiar brownish yellow with gray undertones; in addition, there exists a striking pallor and emaciation. In very severe infections, there is a simultaneous involvement of the palms and soles by a pem-

[38]This author presents numerous excellent illustrations.

[39]E. Hoffmann: Atlas der ätiologischen und experimentellen Syphilisforschung, J. Springer, 1908. Plate 24, Fig. 2; here many other illustrations of congenital syphilis are found.

pemphigoid syphilide, which in typical cases consists of pea-sized vesicles, first clear, then cloudy, and rarely containing blood or pus—the "pemphigus syphiliticus" of the older syphilologists. The vesicles are surrounded by a ham-red to copper-colored zone of infiltration; in contrast to the pyogenic pemphigus of the newborn (impetigo neonatorum) which involves the trunk, the base of the syphilitic vesicles is compactly infiltrated and numerous spirochetes can be easily found in scrapings of the floor of the vesicles.

The coexistence of osteochondritis and pemphigoid syphilides, which at one time was much more frequent, is characteristic of the severe and early diaplacental infections. In such cases in which the pemphigoid eruption extends further and may even involve the entire cutaneous surface, at times a papulocrustaceous syphilide develops, and a visceral syphilis is also present in the liver, spleen, adrenals and in many other organs. The visceral involvements are usually more severe than the cutaneous manifestations; however there is an exception in the case of the pemphigoid syphilide which is a manifestation of syphilis congenita gravis. Between this severe form and the other specific exanthemas, there is a gradual transition, resulting in less severe visceral as well as external symptoms.

The cutaneous manifestations can be very polymorphic, as in acquired syphilis; but their regular sequence and typical morphology may be altered. In children with marked visceral syphilis whose severe fetal infection extends into the nursing age, as Huebner aptly stated, in addition to an irregular, coppery, atypical roseola and palmar and plantar papules, the diffuse, superficial, infiltrated syphilides are an especial indication of recent and severe infantile syphilis. These infiltrations, which may be as large as the palm of the hand, frequently occur on the face, especially around the mouth, and there result in rhagades of varying depth, which later leave characteristic cicatrices (Parrot) as stigmas. Also similar diffuse infiltrations are frequently noticed on the palms and soles and are characterized by their hamlike color. They are less common elsewhere (anus, buttocks). In addition to the coppery, irregular, and frequently atypical roseola, they characterize a severe to medium-severe infection. Macules, maculopapules, and crusting syphilides, which first appear in the less intense infections some weeks and months after birth (syphilis congenita postnatalis), will not be discussed further; they deviate from the appearance of acquired syphilis more or less by their atypical appearance and the absence of the more regular sequences of acquired syphilis. Even ulcerating ecthyma-like syphilides can occur early, and psoriasiform lesions and an infiltrated eruption similar to erythema multiforme[40] (hyperallergy) are also occasionally described, as well as the appearance of infiltrated early gummas.

[40]Stroscher, Dermat. Ztschr. 1910, 17, Plate 3.

Another manifestation is the rare but symmetrical perinychia or paronychia on several or all the fingers, from which spirochetes can easily be demonstrated. These lesions, characterized by a brown to ham-red infiltration, can appear early or late and even become ulcerated; they are pathognomonic of congenital syphilis. With the involvement of one nail and a regional lymphadenitis, a primary lesion of acquired syphilis (A. Fournier's chancre panaris) should be considered; the importance of this is often undervalued.

B. *Other and Late Forms.*—In addition to the cutaneous manifestations, the mucous membranes play an important rôle. Coryza syphilitica is exceptionally important as an early symptom and not infrequently yields proof of spirochetes on dark-field examination. The characteristic "snuffles" of such infants are due to an edema with decreased secretion of the nasal mucous membranes, on which bloody and purulent scabs are also formed; these changes lay the foundation for deeper processes and later malformations of the nasal structure. Other mucous membranes, such as the conjunctivae, are less commonly involved, and sometimes contain spirochetes. Erosions and plaques appear at times in the buccal mucous membrane and can recur later. Rhagades at the angles of the mouth and on the tonsils, which at times are eroded and frequently contain spirochetes, should always be investigated. Experienced syphilologists, such as Hochsinger and others, emphasize the value of a hard enlargement of the cubital and thoracic (paramammillary) lymph glands.[41] In addition to the hutchinsonian triad, Hochsinger considers a somewhat equivalent early triad of congenital syphilis, consisting of skull deformities (caput natiforme, saddle nose, etc.), radiating scars around the mouth (Parrot), and palpable cubital adenopathy. Gland puncture, which is so frequently practiced with acquired syphilis, seldom yields spirochetes in congenital syphilis. However, this practice should not be overlooked in case of doubt.

Alopecia appears diffusely or in small patches, and the involvement of the eyebrows and cilia, as well as the scalp, is particularly characteristic; in older nursing infants and in small children it may be suggestive of syphilis acquisita infantum.

Especially after prenatal salvarsan therapy, superficial manifestations are frequently only minimal or may be absent. Because of this, syphilis congenita tarda may occur in which, after a more or less asymptomatic course, characteristic stigmas and involvements develop later. Besides the hutchinsonian triad of keratitis profunda,[42] nerve deafness, and typical alterations of the upper and middle incisors, as well as of the first molars, there are characteristic or suggestive signs (signs of certainty and probability of the French school), such as

[41] I also advise examination of the lymph nodes in the axillae, etc.

[42] For newer presentation, see Yokota (Zentralbl. f. Haut- u. Geschlechtskr. 51, 589).

widened knee joints, saber tibia (periostitis ossificans), changes of the ocular fundus (frequent, usually chorioretinitis), saddle nose, testicular atrophy, dwarfism or giantism, etc. The various tooth changes, which the young Fournier described in a very exaggerated manner as being produced by the syphilitic virus (microdontia, diastasis, hypoplasia of enamel, irregularity of form), have become much disputed since then. While definite signs are not known for the milk teeth, the real hutchinsonian tooth is typical of the permanent teeth, and is characterized by crescentic identation of the cutting edge, barrel or pear-shaped, screw-driver-like form, and frequently deviation of the converging axis. The collarlike atrophy of the first upper (six-year) molars is, to a certain extent, also characteristic, as well as the so-called Moon's tooth (better described by Pflüger). Other tooth changes should suggest a thorough examination for syphilis; they occur, however, in other morbid disturbances (idiocy, convulsions, etc.). Furthermore, the high arched palate may be mentioned here as a suggestive sign although this condition is more frequently a result of rachitis.

Besides megalosplenia and occasional enlargement of the liver, there are other symptoms in infants which are more or less suggestive: undernourishment, a peculiar pallor, no gain in weight or even a loss in spite of rich food, hydrocephalus, frequent vomiting and crying at night, nervous disturbances and convulsions (with striking venous dilatation, especially on the head). Nephrosis (albumin, edema) seldom occurs.

The manifestations of the so-called period of recurrences (second to fourth year of life), consisting of exuberant condylomas on the genitals and anus, alopecia microareolaris, erosions of the mucous membranes, etc., in vigorous infants, should be considered as syphilis acquisita infantum. Some communications in the literature (chancres in ano and otherwise located extragenitally on the head and face, single or multiple) indicate how difficult the demonstration of chancres can be and how often they are not even considered. Acquired syphilis in infants usually does not run a severe course and, according to the opinions of experienced pediatricians, is rare compared with congenital (and binary) syphilis. This undervaluation of acquired forms of syphilis (condyloma, alopecia, etc.) is in need of revision, as I have often emphasized. It is known that children frequently run a lighter course with otherwise severe infections (e.g. typhus), and the same may commonly be true with syphilis.

C. *Central Nervous System Disturbances (Spinal Fluid Changes) and Other Sequences.*—Important as they may be for the physical and mental development of the child, endocrine dysfunctions and nervous system disturbances can only be mentioned briefly. Many cases of dystrophia adiposogenitalis, infantilism, dwarfism or gigantism, myx-

edema, eunuchoidism, contraction of the visual fields, diabetes, etc., have been explained on this basis, and in this case their treatment may become important.

With regard to the central nervous system, I may say that spinal fluid changes are common in early infancy, but are less frequently encountered later. This difference between early and late infancy may at times be explained by an early death of the severely infected infants, and by a spontaneous or therapeutically conditioned retrogression of spinal fluid syphilis as in acquired syphilis. A special form of spastic involvement is described by Marfan and is manifested in syphilis. In addition to syphilitic meningitis, which can cause hydrocephalus, convulsions, and other signs (paresis, lameness, hemiplegia), there are other more or less obvious defects of the nervous system and disturbances of the intelligence, even to the point of idiocy. Late manifestations occur in the form of juvenile tabes and paresis[43] and become recognizable at the earliest in the fourth year of life; perhaps earlier spinal fluid examination would facilitate its diagnosis and treatment. Involvement of the vessels (arteritis or phlebitis in the brain and elsewhere) is also observed.

Gummas have been observed in all organs. Severe deep tertiary ulcerations often simulate lupus, etc., and can occur on the face, mouth, palate, nose (perforations), and other sites, causing deep ulceration and leaving as stigmas severe mutilating scars, often with bony involvement.

So much for the clinical manifestations, the polymorphism of which has not been completely discussed. When rachitis, tuberculosis, etc., develop along with congenital syphilis in infants, clinical pictures are observed which have given rise to the French theories of syphilis larvée. Here, however, there is the question of a combination of factors whereby in children, weakened through diaplacental infection, other diseases can occur more severely and in peculiar clinical forms. In these cases, specific therapy is often of striking benefit.

V. RECOGNITION AND EARLY DIAGNOSIS

Diagnosis, prognosis, therapy, and, finally, the social problem and prevention of congenital syphilis will now be briefly considered.

Of real help in the recognition of congenital syphilis are:

1. Carefully taken family history.
2. All methods of clinical investigation (inclusive of roentgenograms).
3. Investigation for the presence of spirochetes.
4. Serologic examinations.
5. Spinal fluid examinations.
6. Other methods (luetin reaction, blood sedimentation rate, etc.).

[43] A large number of cases of juvenile neurosyphilis were recently reported by Menninger (Zentralbl. f. Haut- u. Geschlechtskr, 51, 680).

The importance of a thorough history, including that of the parents, siblings and nearer relatives, is universally admitted. It should include all suggestive symptoms (also stigmas) and the investigation of all suspects. French authors emphasize this especially; they have included investigation of all diseases which could be confused with syphilis, and properly so. Further, the history of births (abortion, premature, stillbirth) is very significant, as has already been noted. The placenta, umbilical cord, and macerated fetus should always be thoroughly examined, because they can offer proof or arouse suspicion of congenital syphilis.

A. *Obstetric Aspects.*—An early obstetric diagnosis is extremely important. All pregnant women should be thoroughly investigated clinically after taking their history; but syphilis may be present in spite of negative findings. In addition, it is essential to make a serologic examination of all pregnant women, as far as possible in the fourth month (at the latest at the beginning of the fifth month), always using the standard methods (Wassermann reaction, Kahn test, Müller, Meinicke reaction, and also the sensitive Schreus-Wassermann reaction), which should be repeated in case of inconclusive results. Thus, patients with syphilis can be diagnosed in time for effective treatment to be instituted.

In addition to examination of the retroplacental blood, which seldom shows nonspecific reactions, the placenta and umbilical cord should be thoroughly examined (weight, placental quotient, macroscopic, and microscopic appearance). In all suggestive cases, a thorough search for spirochetes should be made by careful dark-field examinations (tissue scrapings from the vein walls of the fetal and placental ends of the umbilical cord); at times the silver staining of formalin-fixed sections will quickly reveal spirochetes (Armuzzi and others). For this purpose, the preservation of a 5 cm. length of the end of the umbilical cord is advisable, as I pointed out in 1928, for later demonstration of spirochetes by staining of sections. Employing silver stains, my students, Edm. Hofmann, Klaften, Philipp, and others, have frequently demonstrated spirochetes in the fetus and in newborn babies. When negative results are obtained from all of these methods, the investigation of the father and siblings at times may help the physician.

Many suggestions as to the clinical diagnosis have already been given. The differentiation of the simple pemphigus neonatorum (more superficial, noninfiltrated, paler lesions) from the syphiloid pyodermia on the buttocks, etc., is often possible by observation of the lesions, and can be proved by the finding of spirochetes. Although the serologic reactions are extremely important, they should be interpreted with caution during the first ten to fourteen days after birth. Instead of provocative reac-

tions in infants, I advise multiple tests and observations of the serologic curve, which does not decrease as rapidly in the presence of syphilis as it does in the case of false positive reactions.

B. *Examination for Spirochetes.*—Examination for spirochetes is still altogether too infrequent. India ink preparations (E. Müller and others), which pediatricians still use, are inadequate, being much too uncertain. Repeated dark-field preparations of scrapings or tissue serum,[44] which I have employed since 1905 with success, are always advisable since the demonstration of spirochetes on the first trial can be expected only when they are present in large numbers (Jahnel). In addition to vesicles and their floors, papules, erosions, rhagades, etc., the nasal and conjunctival mucous membranes are productive sites for scrapings. For the demonstration of spirochetes in adolescents and in children, I advise scrapings of the palatine tonsils, which frequently harbor spirochetes. In the newborn during the first nine months, no spirochetes can be found in the mouth (Erika Schneider, Eva Löb[45]). Scrapings and small pieces excised from portions of the skin (soles and heels) rich in spirochetes are often easier than obtaining preparations from the base of artificially produced vesicles (cantharides, carbon dioxide snow). For the early diagnosis of asymptomatic syphilis, the nasal mucosae and tonsils should always be thoroughly examined for *Spirocheta pallida* by repeated dark-field preparations. I have already stressed that by this method the diagnosis can be made immediately, while serologic examination requires one or more days. Therefore, the repetition of dark-field examinations is very important.

The luetin reaction is of little significance, and increased blood sedimentation rate is often suggestive but is not decisive.

C. *Roentgen Ray Procedures.*—Roentgen ray examination of the epiphyses of the lower and upper extremities is very important for early diagnosis due to the frequent presence of Wegner's disease. Up to the third month it is pathognomonic; later, confusion may arise with rachitis, Möller-Barlow disease, etc. The essentials of Wegner's disease and of other forms (periostitis, etc.) have been stated previously. Many pediatricians consider roentgen ray examination very important, and this has been confirmed in Germany (Moro, etc.), as well as in France (Péhu).[46] It should always be employed, as well as spirochetal and serologic investigation, especially for the differentiation of congenital from acquired syphilis. At times, hutchinsonian teeth can be recognized in roentgen ray films before erupting through the alveolar ridges. (Stokes, Meyer-Buley[47]). Spinal fluid examination is also important

[44]This alone made it possible for Schaudinn and myself to find *Spirocheta pallida* in 100 per cent of the cases, even in the serum obtained from lymph glands, in March and April, 1905.

[45]Dissertation, Bonn, 1934. In collaboration with my student, Erika Schneider, Löb never found spirochetes in the tonsils or in the mouth before the ninth month.

[46]Cervini and Bogani: Zentralbl. f. Haut- u. Geschlechtskr. 52, 330.

[47]Dissertation, Bonn, 1929, and Dermat. Ztschr. 58: 313.

and to be recommended in cases in which the diagnosis is in doubt. Transient or permanent spinal fluid changes occurring in infants suffice for the definite diagnosis of syphilis. The lumbar puncture is to be preferred to cisternal puncture in small children, the latter needing great skill.

D. *Miscellaneous Facts.*—In consequence of prenatal salvarsan therapy of most pregnant syphilitics, the early recognition of congenital syphilis has become more difficult than formerly. It cannot be doubted that this sovereign therapy, as well as bismuth, is transmitted to the fetus through the placenta in efficacious form, and thus controls or produces a latency of the infection in the fetus. Whether a complete cure or an asymptomatic congenital syphilis results is very difficult to say. Symptoms, or positive serologic (and spinal fluid) reactions, can be absent up to the third or, at times, even to the fifth or sixth month. An examination three months after birth, which many believe to be sufficient, does not suffice for the exclusion of a congenital infection; it is much more practical to demand a follow-up of six months. Infants with normal placental quotients and negative spirochetal findings, who are entirely normal clinically, also should have this supervision if they are born of mothers who have had syphilis or are still syphilitic, even when a sufficient guarantee of cure seems certain due to intensive treatment before or during pregnancy.

Consideration of all of the above mentioned clinical symptoms (lymphadenopathy, splenomegaly, etc.) is again advised. The significance of the stigmas (Hutchinson, Fournier) has already been stressed. Spinal fluid examination is necessary in all nervous disturbances of childhood.

VI. PREVENTION AND TREATMENT

Preventive measures and treatment, as already stated, have produced striking results. In order to reduce the incidence of congenital syphilis, there are two means at our disposal: specific therapy, which has long been well developed and has recently been simplified, and a far-sighted prophylaxis of syphilis in general. This may necessitate making exception to the otherwise valid rule: "Never institute specific therapy without a definite diagnosis."

A. *Preventive Measures of Familial Syphilis.*—The pregnant woman is the sole carrier of the causal agent of congenital syphilis and then only after the fifth month of pregnancy. This is the basis upon which we can and must work for the elimination of congenital syphilis. Because of confused and groundless theories of congenital syphilis ("germinative transmission" and "influence on the germ plasm, i.e., heredity"), the progress made has not been sufficiently great for an effective battle against it. When I presented my above mentioned articles in 1928-29, I tried to show the value of this fact.

The pregnant woman is also the starting point for our measures to reduce syphilis as a generalized affliction. She calls on the physician for other conditions and often for prenatal care. The axiom is then valid: "Always consider syphilis, as well as tuberculosis and cancer." There are social and charitable facilities for the care of pregnant women. Would it not be possible to examine every gravid patient for syphilis before the fifth month of pregnancy, without arousing suspicion? The family physicians of those who do not attend social clinics could also make a fundamental advance, for the sake of healthy future generations, by discreetly conducting a clinical and serologic examination. Thus, all syphilitic women—or almost all—could be reached at the opportune time and the birth of healthy children could be assured.

However, our efforts must extend still further, namely, to the prevention of infection of the mother by the syphilitic father, thus avoiding the introduction of infection into the family, with consequent prevention of familial syphilis in general. Today the attainment of this goal is not so difficult, because salvarsan in sufficient dosage quickly and efficiently checks the spirochetes which migrate to the surface and are thus capable of transmitting the disease. This rapid reduction of the danger of inoculation is also important for the reduction of familial syphilis, because infected men, with recently acquired syphilis, who allow themselves to be treated immediately, usually do not transmit their infection, even during treatment. I advise immediate treatment for women who have been exposed and probably infected by husbands whose syphilis is still infectious, even if proof of the spirochete is not found either in a cervical smear or elsewhere (urethra, tonsils, etc.). For these possible, indeed probable, infections of short duration, the preventive treatment of one or two courses with short rest periods will suffice, provided that the serologic reaction remains negative on repeated examinations. Thus, the danger of familial syphilis is banished, and the possibility of congenitally syphilitic offspring is eliminated.

However, if that is not feasible, there remains the possibility of accomplishing not only the healing of the gravid mother, but also the birth of a healthy child by means of treatment during pregnancy. Our three-course system (Bonn) suffices for a final cure of early syphilis if it is not too old and unusually stubborn, which, however, our experience seldom shows to be the case. I emphasize again, along with experienced obstetricians, that this treatment, instituted early enough in the second half of pregnancy, should continue until parturition, in order to avoid danger of premature termination. A new course of treatment is not necessary in later pregnancy in women who have been treated intensively and systematically and whose cure may be assumed with sufficient probability. In my article, "Is Syphilis Curable?"[48]

[48] "Ist Syphilis heilbar?" Dermat. Ztschr. 59: 279, 1930.

I have explained the signs which are to be considered as indicating cure and a sufficiency of treatment; the publications of Zieler[49] may also be referred to in this connection.

A further simple measure for the prevention of familial and congenital syphilis is to advise the use of accepted methods of venereal prophylaxis by husbands who indulge in extramarital relations. Also, anticonceptional prophylaxis is to be recommended, that is, the conscious avoidance of impregnating syphilitic women until they have been sufficiently treated. If, in spite of this, pregnancy ensues before complete cure appears to have been accomplished, the prenatal treatment advocated under all circumstances by so many obstetricians must be carried out through the period of pregnancy, in order to ensure the birth of a healthy child.

B. *Prenatal and Preventive Treatment.*—It has been our experience in general that two combined courses with a four-week rest period suffice for the prenatal treatment of the fetus, even in the presence of obvious syphilis. The assumption that gravid women after an initial dose of 0.3 gm. cannot tolerate individual doses of 0.45 gm. of neoarsphenamine twice a week (thus 0.9 gm. weekly doses) is not in accordance with our long years of experience.[50] Ten or, better still, twelve injections combined with bismuth constitute a course. Even larger doses of neosalvarsan (0.52 and 0.6) have been given to vigorous pregnant women in my clinic without any disturbance. The normal dose of 0.45 gm. twice weekly ordinarily suffices to safeguard the fetus.

Frequently the mother as well as the child cannot receive this complete course during pregnancy, and are thus undertreated. These partially treated mothers and newborn babies must receive further therapy until the entire course has been given.

That leads us to the question which I brought up years ago, as to whether a preventive treatment of the newborn is advisable before the syphilitic infection can be definitely demonstrated. I have affirmed this for a long time and have found much support. Today, since the prenatal treatment has been further extended, a preventive treatment, representing only a continuation of that instituted prenatally, may be required. After the delivery, the mother and child are in the hands of the physician and, with sufficient explanations, should be amenable to proposals for therapy; later, it is more difficult to persuade the mother to continue treatment. Valuable time is lost and the chance of an early cure is decreased[51] with expectant observation. The damage which can occur from too intensive treatment is slight; much greater is the danger of further involvement which requires difficult and pro-

[49] International Derm. Congress, Budapest 1935.

[50] In many countries (Japan, Java) the tolerance seems to be less (German preparations?).

[51] The publications of the Spiethoff clinic do not alter this standpoint; the customary treatment of salvarsan alternating with other preparations is the basis of the Bonn system, which has also been accepted in Denmark, Austria, Spain, etc.

tracted treatment, and which can have further sequelae, while the prognosis becomes poorer the longer one waits. A six-month observation period, therefore, is necessary in order to ascertain freedom from syphilitic involvement.[52]

That is basis enough to justify the preventive treatment of all newborn children of mothers who are still infectious or in whom infection is suspected. This should begin immediately after birth, if they have received inadequate, or no prenatal therapy. This standpoint is well grounded, because it offers the most for individuals and family, as well as for social-hygienic indications, and would contribute efficiently to the limitation of syphilis. Much care and expense is saved by such a procedure. Finally, babies, in whom the presence of syphilis is not definitely established, withstand antisyphilitic treatment very well, according to our experience. Against the advantages enumerated, a few really healthy infants will be treated. Their number will weigh slightly with most experienced physicians; furthermore, simple stovarsol therapy is regarded as sufficient by many clinicians.

C. *Postnatal Therapy.*—While I have seen good results from combined neosalvarsan-bismuth (or mercury) therapy with medium dosage (.01 gm. neosalvarsan per kilogram), recently stovarsal[53] treatment has been preferred by most pediatricians, gynecologists, and dermatologists and has been regarded as sufficiently efficacious. An intensive ninety-four-day course has been advocated by E. Müller, after he had previously—like myself—interceded for a very intensive combined calomel-neosalvarsan therapy. Also, I have employed the stovarsol therapy occasionally usually, however, with bismuth injections (0.002 to 0.003 gm. metallic bismuth per kilogram) or mercury inunctions. Details are given in my textbook of dermatology.[54]

E. Müller advises stovarsol therapy alone with large doses for ten days with four-day rest periods between (first dose, ½ tablet of 0.25 gm.; with vigorous infants, 1 tablet, and then a rapid increase to 2, 3, or 4 tablets daily). With a course of 7 x 10 = 70 treatment days and 6 x 4 = 24 rest days between, he tries to give 40-60 gm. of stovarsol and thus conclude the treatment in ninety-four days. With this treatment, the children become and remain healthy and serologically negative.

Other noted pediatricians advise beginning with small doses, then increasing slowly from ¼ to ½, ¾, and 1 tablet of 0.25 gm. in order to employ larger doses, according to tolerance, after the second or

[52]Recently, Coppolino advanced the opposite view, that children, who presented no clinical, serological and roentgen findings one month after birth, did not require treatment. (Zentr. Bl. Hautkr. 52, 63).

[53]No. 594 of Ehrlich's series is called spirozid in Germany, stovarsol in France, and acetarsone by the American Medical Association's "New and Non-Official Remedies." The tablet is 0.25 gm. by weight (translator's note).

[54]E. Hoffmann: Behandlung der Haut- und Geschlechtskrankheiten, ed. 5, 1930, new edition in preparation.

third weeks; many combine this with mercury inunctions (0.1 gm. of 33 per cent ointment per kilogram) or bismuth injections. The total of the stovarsol—with or without short rest periods—amounts to from 24 to 30 gm.; by repetition of this course during the first half-year twice, and in later months even three times, this total can be reached.

Tolerance is usually high with good care and nourishment (as far as possible with mother's milk) and dosage suitable to the individual case; complications, such as vomiting, diarrhea, and exanthemas, are rare and can be controlled by suitable means (sodium thiosulphate). Severely involved newborn and infants occasionally die sooner, due to too intensive specific therapy (spirochetal toxicity), which deaths are no great misfortune since the infants would probably be backward physically and mentally. Preliminary small doses of mercury protiodide or several mercury inunctions and cautious stovarsol doses are suggested. Heavily infected infants, and preferably all, should at first be treated in hospitals. After retrogression of symptoms, and provided there is good tolerance, the simple stovarsol therapy can be continued as an out-patient treatment.

Stovarsol is not sufficiently efficacious for the prenatal treatment of pregnant women and is, therefore, no more permissible than malaria therapy during gravidity (transmission of plasmodia).

According to most experienced syphilologists, intensive stovarsol therapy, with dosage and duration adapted to the severity of the congenital syphilis, is very effective and so efficacious that neither recurrences nor nervous involvements ensue. Mental deficiency due to severe fetal infection cannot always be prevented,[55] but sufficient prenatal neosalvarsan and bismuth therapy must be given in order to make this prevention possible. Older infants and small children, as well as adults, should be treated by neosalvarsan (0.01 per kilogram) and bismuth as outlined in my book. In cases in which stovarsol is not sufficient, this treatment is to be advised and may be repeated once or twice, according to indications. The saturation therapy of Schreus or, better still, malaria followed by the Bonn method of therapy, should be considered.

Minor late involvements of other types do not always require intensive salvarsan-bismuth therapy; here, iodine and bismuth therapy suffice, especially if it is a quiescent noninfectious process or a benign-appearing latent process (positive serologic reaction).

One more word about the intensity of the treatment. We have already mentioned that congenital syphilis shows a characteristic tendency toward spontaneous healing; thus, spinal fluid changes and visceral processes, with the exception of the bony involvement of Wegner, often disappear entirely, or to a large extent. It remains undecided whether, as a consequence of the growth process, infants and small children

[55] Recently, Kis and Rajka advised stovarsol therapy immediately after birth for all children of syphilitic parents, especially as a means of preventing defective intelligence.

possess a particular resistance to agents of infection, such as the *Spirocheta pallida,* but syphilis acquisita seldom runs a serious course. At all events, an excessively large dosage of stovarsol and neosalvarsan does not appear necessary because here the aid of *vis medicatrix naturae* can perhaps be relied upon. Therefore, in spite of my inclination for the maximal dosage, I have usually avoided dosages of more than 0.01 gm. neosalvarsan per kilogram and have usually had success with these small doses. Large doses, approaching the limit of tolerance, are not necessary with stovarsol; indeed, the goal at which maximal therapy aims, namely, a complete cure in a limited time, need not be considered.

VII. CONCLUSIONS

Great advances, which justify further hopes, have undoubtedly been attained during thirty years of etiologic and twenty-five years of therapeutic investigation. The specter of "hereditary syphilis" and "hereditary dystrophies," as well as "hereditary corruption" has been banished.[56] The pregnant woman has been recognized as the sole intermediary for the transmission of congenital syphilis. The danger of transmission of spirochetes to the fetus is first present during the fifth month of pregnancy. This is the definite basis upon which we can lead an effective battle. Through suitable medical and social care, we must succeed more and more in getting in contact with all syphilitic pregnant women before the fifth month. With two prenatal courses of treatment extending from the middle to the end of pregnancy, healthy children can be produced, who are, and remain, free from signs of mental and physical inferiority.[57] Postnatal preventive therapy administered to apparently healthy children, born of infected or infectious mothers, is justifiable and later avoids much affliction and expense. Postnatal therapy of infected children has been simplified by stovarsol therapy which, according to the opinion of experienced clinicians, is efficacious; I have had good and lasting results with it, when combined with bismuth (or mercury) and neosalvarsan therapy.

The introduction of syphilis into the home can best be precluded by the preventive treatment of women who have been exposed to it. Measures have been suggested for the treatment of the infected man before marriage, in order to avoid the misfortune of familial syphilis. After getting in touch with the syphilitic pregnant woman, by means of her history and family investigation, further infectious cases can be traced and treated. By this procedure, which has been supplemented

[56]Husler has discussed, but leaves open, Lenz's question of whether treatment of the parents by iodides, mercury, and arsenicals could influence, by heredity, the progeny: such an apprehension is as groundless as the presumption that syphilitic toxins could influence heredity.

[57]Husler (Ztschr. f. Kinderh., 43: 555, 1927) has never found syphilis in the third generation. I allowed Feige to discuss this subject in his dissertation (Bonn, 1917): a syphilitic blastophthoria was never evident, nor even surmised. The physical and mental condition of forty-two congenital syphilitic adults was found by Husler to be above the average.

in most civilized countries by the formation of regulatory laws for the control of venereal diseases, and by the sympathetic cooperation of gynecologists, dermatologists, and pediatricians, a further diminution must result in the incidence of congenital syphilis and of acquired syphilis.

The definite reduction of congenital syphilis, as shown by yearly census in Denmark,[58] to about one-tenth the former number in twelve years, with elimination of stillbirths and severe forms of the disease, must be an inspiration to us to continue the eradication of this disease which was once so greatly feared. The Danish and German results have been attained with German salvarsan preparations, the efficacy of which has been proved in the Ehrlich Institute at Frankfort;[59] I have no experience with other arsenobenzine products. As the elimination of leprosy was accomplished in civilized lands in the Middle Ages without a specific therapy, we may hope for a still greater success in the battle against syphilis, with the aid of our modern knowledge of early diagnosis and treatment. The marked decrease of congenital syphilis and the elimination of its severe forms give us great confidence that we are on the right path and will be victorious. This goal would be reached still more quickly if the intensive combined treatments with short rest periods, shown by statistics to be most effective, were universally[60] employed and if preventive therapy were more accepted.

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[58] Lenstrup (Copenhagen) stated on the basis of 250 congenital syphilitic children that syphilis is not the cause of imbecility; instead, it is due to hereditary inferiorities of other types. Therefore, he proposed the sterilization of such individuals (Sixth Northern Congress of Pediatrics, August, 1934).

[59] E. Hoffmann, Über die zweckmäszigste Behandlung der Syphilis (Wien. klin. Wchnschr. 1935, 1010). It remains to be decided whether the recently recommended solusalvarsan is as good as the standard neosalvarsan.

[60] Particulars are given in the article mentioned in the preceding footnote (59).

EDEMA ASSOCIATED WITH HYPOGENESIS OF SERUM PROTEINS AND ATROPHIC CHANGES IN THE LIVER

With Studies of the Water and Mineral Exchanges

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RECENT advances in our knowledge concerning the physiologic mechanisms involved in the exchange of body fluids have greatly heightened our interest in cases of so-called "idiopathic edema." It is obvious from an examination of published case reports that a variety of etiologically unrelated clinical entities have inadvertently been grouped together under this general designation merely because the origin of the edema in each instance has been undetermined. As a tentative diagnosis, therefore, "idiopathic edema" simply signifies that all known causative factors, such as nephritis, nephrosis, circulatory insufficiency, inflammatory and allergic disorders, severe anemia, protein starvation and the excessive ingestion of sodium chloride and water, have been excluded.

The present report deals with a case falling into this general category, which was the first of its particular kind to be recorded, so far as we are aware. As indicated in the above title, the underlying pathogenesis of the edema in this instance involved a marked degree of hypoproteinemia believed to be due to a deficiency in the physiologic mechanism for fabricating serum proteins. The postmortem discovery of a peculiar zonal atrophy in the liver lobules suggests the likelihood that this was the responsible pathologic lesion. Since our preliminary presentation of this case,[1] Myers and Taylor[2] have reported interesting clinical studies on a man fifty-one years of age, who was likewise suffering from chronic hypoproteinemic edema apparently due to an inability to produce serum proteins at a normal rate. During the past few months we have had the opportunity to observe an additional child presenting a somewhat similar clinical picture. It is not unreasonable, therefore, to believe that this entity will be recognized with increasing frequency, if searched for among the assortment of cases ordinarily classified under the designation, "idiopathic edema."

CLINICAL FEATURES OF CASE

The patient, E. N., was a girl two years of age, who was admitted to the Pediatric Service of the University of Minnesota Hospital on Oct. 5, 1931, because of intractable, generalized edema. According to her past history, she was delivered

From the Departments of Pediatrics and Pathology, University of Minnesota.

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at term, weighing 9 pounds. Labor was "dry" and was prolonged to thirty-six hours. The face was observed to be swollen at the time of birth. This did not persist, however, and so was in all probability merely a result of difficult labor. Her early infancy was not remarkable except for frequent attacks of coryza. She was fed at the breast for nine months but was given cow's milk in addition after the first month. Cod liver oil and orange juice were given regularly after the first few weeks of life, and cereals and vegetables were added after the fifth month. After she was weaned from the breast, standard diets appropriate for the age were given. It is worthy of special note that her feeding and general care were under the supervision of a competent pediatrician throughout her entire life before she was

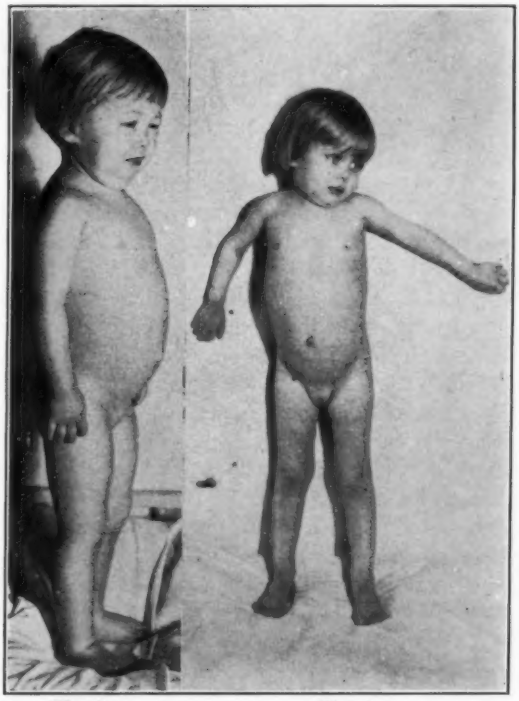

Fig. 1. Fig. 2.

Fig. 1.—Showing persistence of edema nearly five months after admission to the hospital in spite of high-protein, "salt-free" diet.

Fig. 2.—Appearance of patient after loss of edema and ascites as a result of blood transfusion.

referred to us for special study and treatment. Her development and growth were essentially normal. She walked at fourteen months and learned to talk shortly thereafter. She perspired unusually freely and always tended to be somewhat constipated. In all other respects she seemed to be essentially normal up to time of the present illness. The family history was not remarkable. Her parents, who were of Bohemian extraction, were both fairly healthy. She had no brothers or sisters.

Present Illness.—Edema of the face and extremities sufficiently marked to attract the attention of her parents first appeared in January, 1931, following a "cold." This edema persisted without much change until March, when it ap-

parently subsided partially during an attack of whooping cough. Soon thereafter, however, it recurred and by July had become fairly marked. In September it was observed that the abdomen had enlarged considerably and the edema of the face and extremities had become still more conspicuous. Because of increasing irritability and abdominal discomfort, the patient was admitted to the University Hospital for more intensive study and treatment.

It is worthy of special emphasis that her diet had always been adequate as regards its protein and vitamin content. At no time was there any demonstrable evidence of cardiac, renal, or hepatic disease. Shortly after the first appearance of edema, when the patient was but fourteen months of age, the urine was examined carefully for albumin, casts and blood cells, but no abnormalities were found. Repeated examinations thereafter likewise yielded negative results.

On admission the patient appeared very much as she did when the photograph shown in Fig. 1 was taken. The general physical examination was essentially negative except for the obvious edema and abdominal enlargement. The edema was generalized but was more in evidence over the face and extremities than elsewhere. Protrusion of the abdomen was clearly due to the presence of freely shifting fluid. The texture and color of the skin and mucous membranes were essentially normal. The tongue was not enlarged. The hair was normal in amount, texture, and distribution. Except for fairly marked edema of the eyelids and slight hypertrophy of the tonsils, the eye, ear, nose, and mouth examinations were negative. Temperature was normal. *Heart:* Size, action, sounds and response to effort were entirely normal. Systolic blood pressure was 106 and diastolic, 72. Eyegrounds appeared normal. Lungs were clear. Nervous reflexes were all normal. *X-ray* examinations of the wrists, arms and legs showed her bone development to be normal. The urinary tract showed no abnormality by x-ray. The *urine* was negative for albumin, casts, blood cells, and glucose. Specific gravity ranged between 1.010 and 1.030. Phenolsulphonephthalein test showed 50 per cent excretion in two hours on one occasion and 60 per cent on another. *Blood Findings:* The Wassermann test was negative; nonprotein nitrogen 22.5 mg. per 100 c.c. The serum proteins were: albumin 1.9 per cent, globulin 1.5 per cent, total protein 3.4 per cent; plasma cholesterol 226 mg. per 100 c.c.; plasma chloride 357 mg. per 100 c.c.; serum calcium 11.25 and inorganic phosphorus 5.58 mg. per 100 c.c. Unfortunately fibrinogen was not determined, but the coagulation of the blood appeared to be entirely normal. Blood counts were as follows: erythrocytes, 4,480,000 per c.mm.; hemoglobin, 87 per cent; total leucocytes, 8,300 per c.mm. with 78 per cent polymorphonuclears, 17 per cent lymphocytes, 4 per cent eosinophiles and 1 per cent large mononuclears. Platelet counts were not made.

Clinical Course.—Because of the intractable nature of the edema and because her home lacked facilities adequate for her care, the patient was kept in the hospital for a period of 201 days, during which the special studies reported here were carried out. The urine remained albumin-free throughout this entire period except for a trace found in a single

sample at the height of her terminal infection. Except for a brief period following blood transfusion, the edema persisted in spite of a high-protein, low-salt, vitamin-rich diet and a constantly positive nitrogen balance. During the greater part of this period, she consumed daily between 2.5 and 3.5 gm. of protein per kilogram of body weight. Variations in the degree of edema occurred as a result of special procedures being tested, but none of the latter appeared to stimulate regeneration of the serum proteins. That the edema was due to a reduction in the colloidal osmotic pressure of the blood incident to marked hypoproteinemia was proved by its complete disappearance following blood transfusion, which raised the serum proteins above the critical level. Figure 2 shows the patient several days after the transfusion, when no edema was demonstrable. After a remission of a few weeks' duration, she again showed a

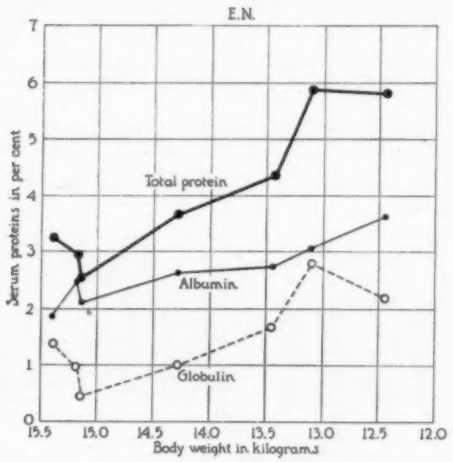

Fig. 3.—Showing inverse relationship between concentration of serum proteins and degree of edema, as indicated by changes in body weight.

gradual gain in weight due to retention of fluid. After the edema had become apparent at the end of seven weeks, it was discovered that the serum proteins had again declined toward the original low level. At no time did the serum globulin fraction exceed the albumin in amount. The close relationship between the serum proteins and the degree of edema, as indicated by changes in body weight, is shown in Fig. 3.

WATER AND MINERAL EXCHANGES

Obscurity regarding the underlying pathogenesis of this unusual form of hypoproteinemic edema suggested the desirability of measuring the water and mineral exchanges under a variety of conditions. The individual effects of parathyroid extract, of posterior pituitary extract, and of blood transfusion are shown in the accompanying charts, which are largely self-explanatory.

The methods used for measuring the water balance were those which we have employed in previously reported studies.[3] In brief they were as follows: The patient was kept in a special metabolism room in which the temperature was maintained between 67 and 74° F. and the relative humidity between 40 and 60 per cent at all times. A specially trained nurse supervised the administration of all food, drink, and medication, collected excreta, checked the room conditions and weighed the patient on a Troemner balance. During periods of special study the daily diet, which was given in four equal meals at six-hour intervals, was made up of powdered whole milk, egg yolk, egg white, cane sugar, clear lemon juice, and water. At other times the patient was given in addition meats, vegetables, fruits, yeast, and cod liver oil. Stools were separated by means of carmine given at the beginning of each period. They were dried to determine the water content. The

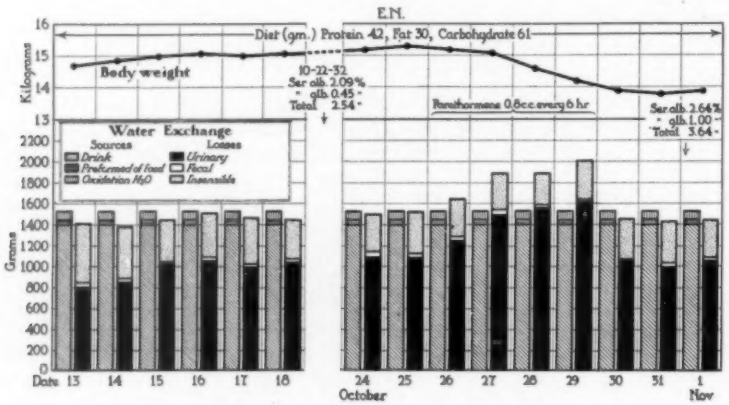

Fig. 4.—Partition of water exchange before and during administration of parathyroid extract. The latter is seen to cause a moderate reduction in edema in spite of low serum protein concentration.

insensible water loss of the body was calculated from body weight changes and a rough estimate of the metabolic mixture according to the method of Newburgh, Johnston, and Falcon-Lesses.[4] Serum proteins were determined according to the procedure of Howe as modified by Hawk and Bergeim.[5] The methods used for determination of the various minerals of the urine and stools were as follows: Sodium, Butler and Tuthill[6]; potassium, Shohl and Bennett[7]; chloride, Volhardt, as modified by Harvey[8]; phosphorus, Fiske and Subbarow[9]; calcium, Tisdall and Kramer[10]; and nitrogen, Kjeldahl.[11]

The data presented in the first part of the chart shown in Fig. 4 are typical of the water balance throughout the greater part of the patient's sojourn in the hospital. The measurements recorded are presented merely as a sample to illustrate the fact that edema persisted in spite of a "salt-free," relatively high-protein diet. It will be observed that

the total serum protein was barely half the value usually cited as approximating the critical level below which edema develops. In contrast to the reversal of the albumin-globulin ratio, which is characteristic of nephrosis, the globulin fraction was reduced to a greater degree than the albumin in this instance.

The effect of parathyroid extract (parathormone), as shown on the right half of the chart, was fairly effective in producing a negative water balance during the period of its administration. It is apparent that the negative balance was due exclusively to an increase in the urine volume. While the concentrations of both the albumin and the globulin of the serum were found to be somewhat increased following the period

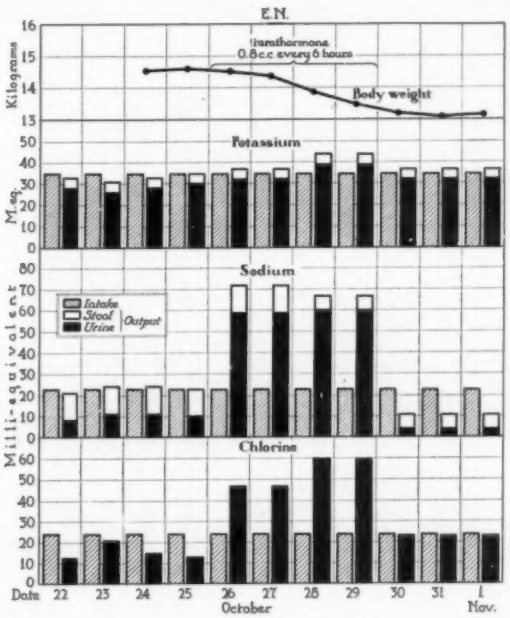

Fig. 5.—Effect of parathyroid extract on potassium, sodium and chlorine excretion.

of diuresis, they were not elevated above the "critical level" for edema formation. In fact, the extra water lost as a result of the administration of parathyroid extract was regained within a few days after withdrawal of the hormone.

In Fig. 5 are charted the intake and output of potassium, sodium, and chloride before, during, and after the period of parathyroid extract administration. That most of the edema fluid lost during the diuresis period was extracellular in origin is indicated by the excessive loss of sodium and chlorine. The slight negative balance of potassium during the third and fourth days may indicate a small loss of intracellular water during that portion of the period, but the amount is comparatively in-

significant. Following omission of the parathyroid extract, sodium began at once to show a positive balance, whereas the intake of chloride and potassium was equalled by the output. These observations merely indicate that the composition of the edema fluid in this case is essentially the same as that found in other forms of edema.

The effects of parathyroid extract on the calcium, the phosphorus, and the nitrogen balances are shown in Fig. 6. It will be seen that the nitrogen output remained unchanged. It is especially notable that the patient remained in positive nitrogen balance during the succeeding five months also, but failed to maintain her serum proteins at a level sufficiently high to prevent edema. The output of calcium and phosphorus by way of the kidneys and the intestines was significantly in-

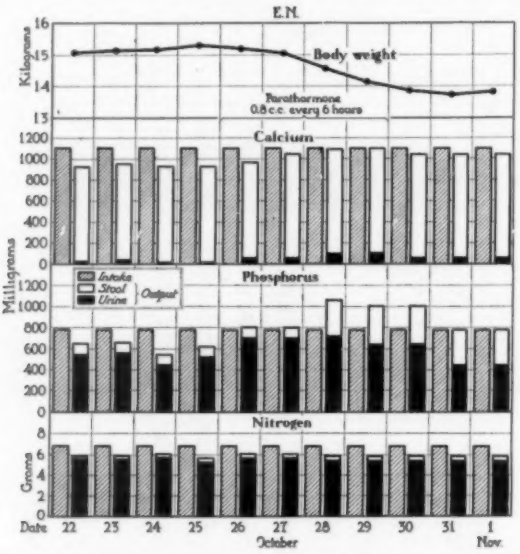

Fig. 6.—Effect of parathyroid extract on calcium, phosphorus and nitrogen balances.

creased by the hormone. Whereas the total calcium excretion had been definitely below the intake previously, the two were essentially equal during the parathormone period. The positive balance of phosphorus noted in the foreperiod was superceded by a definitely negative balance when the extract was administered. Unfortunately serum calcium and protein determinations were not made at the height of the period of diuresis and so it is impossible to say whether or not the degree of blood concentration was sufficient to explain the parathormone diuresis alone on an osmotic pressure basis. The nitrogen, the calcium, and the phosphorus excretion studies throw no light on this phase of the subject, but merely indicate that the patient's response to the extract was entirely normal as regards the calcium and phosphorus metabolism.

Because it had previously been found possible to cause loss of edema in certain cases of nephrosis by the administration and withdrawal of pitressin, the antidiuretic principle from the pituitary gland,[3] the procedure was carried out in the case of this patient. While she responded

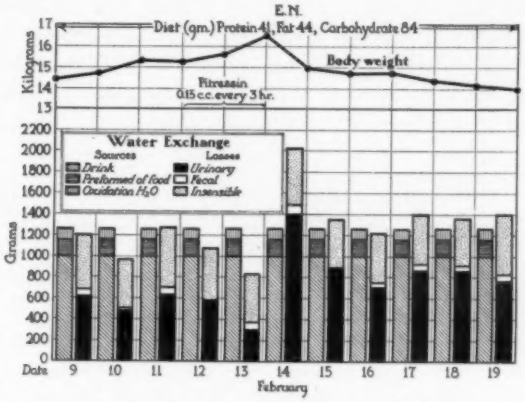

Fig. 7.—Effect of sustained pituitary antidiuresis and withdrawal on the water exchange.

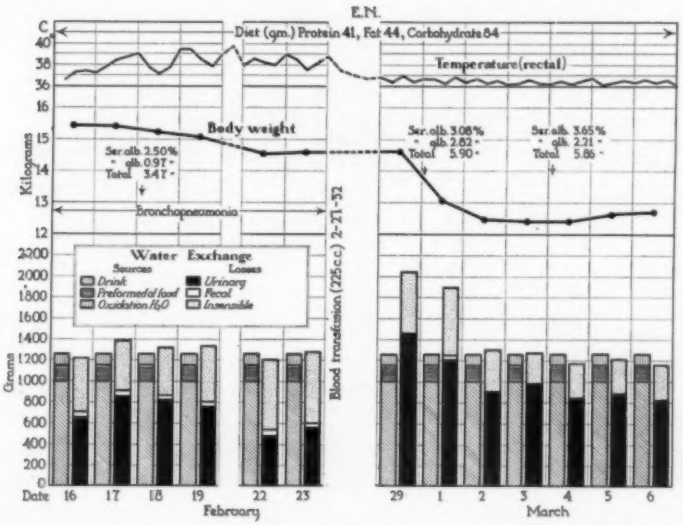

Fig. 8.—Effect of blood transfusion on the serum proteins and the water exchange. Rapid loss of edema fluid.

to the sustained pituitary antidiuresis like other edematous subjects do, that is by a gain in body weight and an obvious increase in the degree of edema, her response to withdrawal of the hormone differed from that of the other patients mentioned in that the period of active diuresis was

not sufficiently prolonged to result in a significant net loss in body water. This failure was probably due to the fact that her serum proteins totalled less than 3.0 per cent at the time of the test.

The causative relationship between the depressed level of the serum proteins and the occurrence of edema is strikingly shown in Fig. 8. During the course of a mild attack of bronchopneumonia, the patient was given a fairly large transfusion of blood. Following a latent period of nearly two days, active diuresis set in. This resulted in a net loss of 2.3 kilograms of edema fluid within forty-eight hours. The total serum

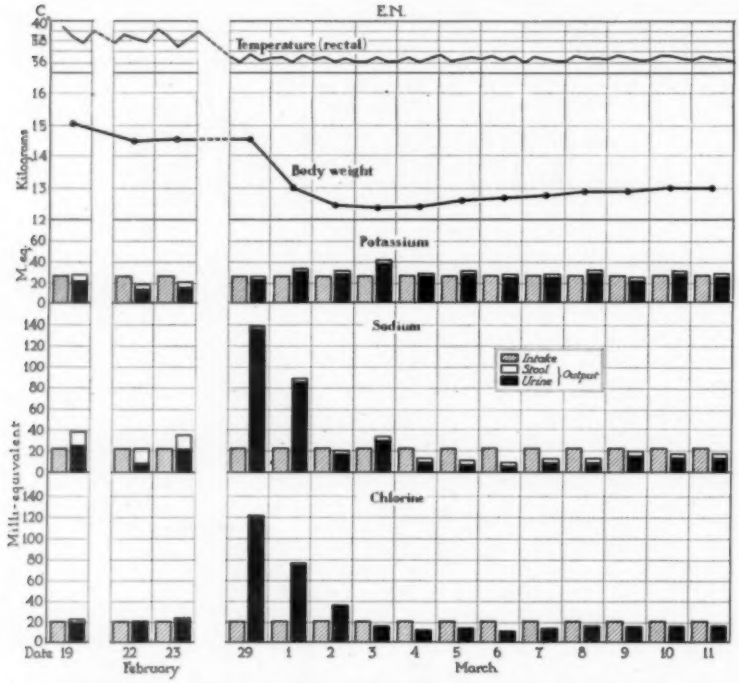

Fig. 9.—Potassium, sodium, and chlorine losses accompanying excretion of edema fluid after blood transfusion.

proteins were increased from approximately 3.5 to 5.9 per cent as a result of the transfusion. Since the serum protein value, 5.25 per cent ± 0.25, may be regarded as the critical level below which edema develops, it is reasonable to assume that the elevation in serum protein level is alone sufficient to account for the result obtained. No adequate reason can be offered at the present time for the delay in appearance of diuresis following the transfusion.

It is obvious from the chart that practically all of the extra water lost was excreted by the kidneys. It will be observed that the amount

of water lost as insensible perspiration was significantly greater when the patient was edematous than it was after the edema had disappeared. Since the insensible water loss has been shown by Gilman and Barbour[12] to be inversely proportional to the osmotic pressure of the blood plasma, this observation might be interpreted as indicating a decrease in the value of the latter during the edema period, when the patient was on a low sodium chloride intake. The subject should be further investigated in patients with edema receiving various amounts of salt in the diet.

The mineral exchange data presented in Fig. 9 show that the water lost during the period of diuresis was derived from the extracellular fluid compartments of the body because the balances of sodium and chloride were strongly negative. In contrast the potassium balance

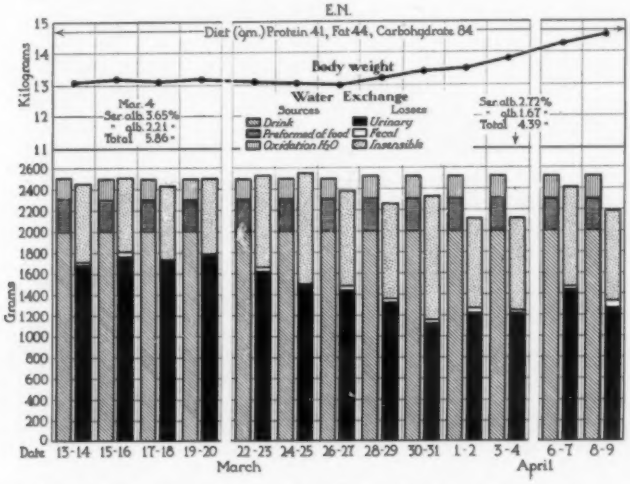

Fig. 10.—Water exchanges in posttransfusion period in two-day periods. Occurrences of edema associated with lowering of serum proteins in spite of high-protein diet.

was but slightly altered. There was, nevertheless, a definite, though slight, increase in the excretion of potassium, which persisted well beyond the period of active diuresis. This might be interpreted as indicating a small outward shift of intracellular water.

Following a slight increase within a few days after cessation of diuresis, the body weight remained essentially stationary for approximately three weeks, as shown in Fig. 10. Thereafter, it rose gradually because of the recurrence of edema. Determination of the serum proteins after reappearance of edema showed their total value to have fallen somewhat below the accepted critical level for edema formation. The rather long period of freedom from edema following a single transfusion and the apparent gradualness of serum protein decrease suggest a slow

loss of the circulating serum proteins by ordinary "wear and tear" rather than by an active destructive process. Since the ascitic fluid present had but a low protein content and the urine contained no protein, it appears almost certain that the underlying defect lay in the patient's inability to form new serum protein molecules at a normal rate.

During her long period of hospitalization the general clinical picture remained essentially unchanged except for one mild attack of pneumonia, which she survived, and a later acute attack of unilateral otitis media with complicating mastoiditis. Following operation for the latter, the patient again developed bronchopneumonia from which she died on April 23, 1932. The total period covered by this latter episode was but a few days.

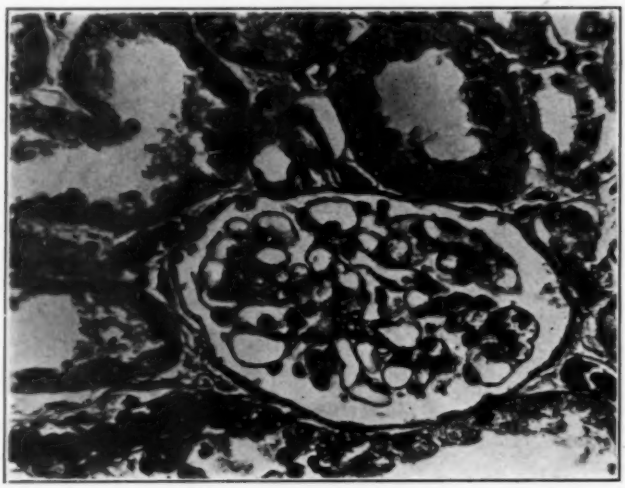

Fig. 11.—Section of the kidney. Note that the glomerulus and the tubules are entirely normal. Photomicrograph.

POSTMORTEM EXAMINATION

Grossly the postmortem examination was negative, except for purulent exudate draining from the mastoid wound, early bronchopneumonia, and the presence of a moderate degree of generalized edema with excess of translucent fluid in the serous cavities. The *heart* was of normal size and development and appeared to be entirely free from acute and chronic disease. The *kidneys* were normal in size. The capsule was stripped from the cortex with ease, leaving a normal appearing surface. Microscopic sections (Fig. 11) showed that both tubules and glomeruli were entirely normal. The endothelial cells were small and inconspicuous, as they are normally in a child, and there was no thickening of the capillary basement membrane. The tubules contained no precipitated protein, and

the tubular cells were entirely normal in every respect. There was no evidence of disease in the interstitial structures.

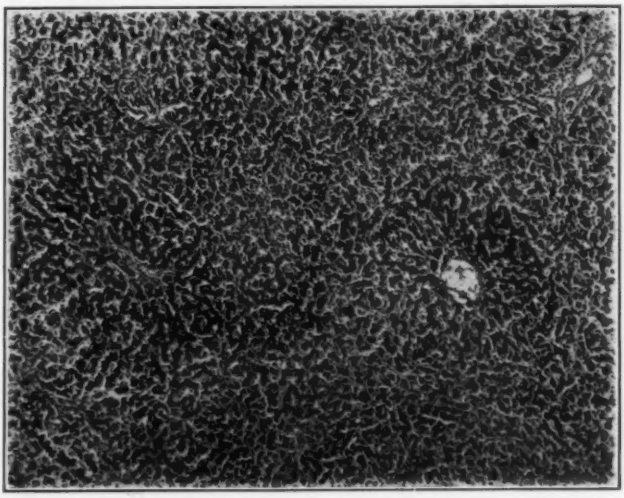

Fig. 12.—Section of the liver under low magnification. Note the persistence of the hepatic cords about the central veins and the extensive atrophy in other parts of the lobules. Photomicrograph.

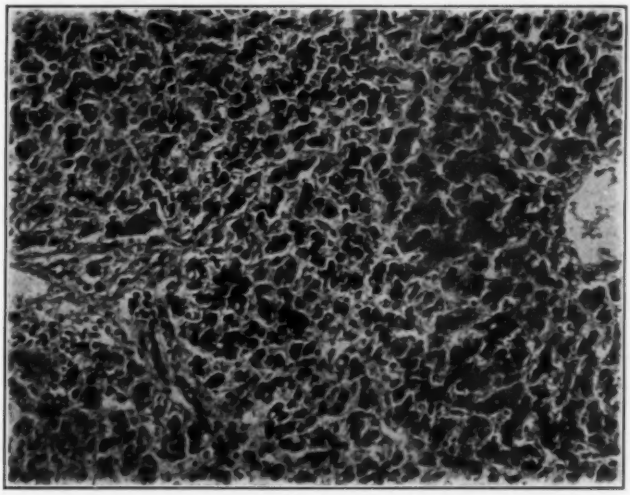

Fig. 13.—An area from Fig. 12 under moderate magnification. Note the preservation of the hepatic cords adjacent to the central vein (on the right side of the illustration) and the atrophy of the intermediate and peripheral zones of the lobule. Photomicrograph.

While the *liver* appeared normal macroscopically, a microscopic study revealed striking changes. Under low magnification (Fig. 12) a marked

atrophy of the hepatic cords, especially in the intermediate and peripheral zones of the lobules, could be seen. The hepatic cells about the central veins were usually intact. In Fig. 13 a part of a lobule is shown under higher magnification. The central vein is shown on the extreme right of the photomicrograph. The hepatic cords around the central vein were practically normal in appearance, while the cords in the intermediate and peripheral zones were broken and discontinuous. A portion of the atrophic zone of a lobule is shown in Fig. 14. It will be noted that the hepatic cords did not form a continuous network, an appearance evidently due to the complete degeneration and disappearance of adjacent cells. Fragments of necrotic cells could be seen, but there was no evidence of a diffuse necrosis of cells such as is seen in acute atrophy

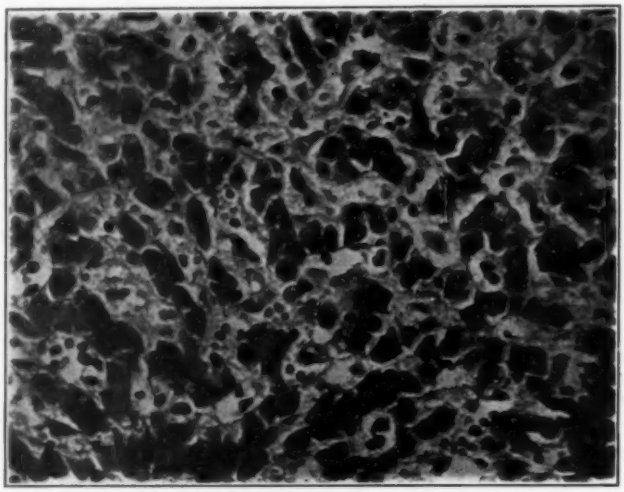

Fig. 14.—An area from the intermediate zone of a lobule under high magnification. Note the discontinuity of the hepatic cords due to the disappearance of a great many liver cells. Many cells are decreased in size and their surfaces are rounded because of absence of adjacent cells. Photomicrograph.

of the liver. The microscopic appearances were rather those of a chronic progressive atrophy of the hepatic cords. In some sections of the liver, lobules were found which showed instead of atrophy occasional small necrotic foci. The atrophy described above was, therefore, not uniform in degree throughout the liver. No explanation for the unusual lesion was found. It differed from the common forms of acute atrophy in the absence of extensive areas of nercosis. It was unlike subacute and chronic atrophy in that there was no cirrhosis. In states of prolonged severe malnutrition appearances similar to those in this case may occur. However, it is perhaps best to classify this disease as *primary atrophy of the liver*, i.e., one of undetermined etiology.

DISCUSSION

The features of special interest in the foregoing report are two: (1) that pertaining to the nature of the hypoproteinemia which was responsible for the edema and (2) that concerning the unusual pathologic lesions in the liver. Two unusual points regarding the serum proteins should be emphasized. The more important is that this patient manifested an unmistakable deficiency in her mechanism for fabricating these important blood constituents. This appears to us to be definitely proved by the fact that marked hypoproteinemia persisted over a period of many months in spite of a high-protein diet with constant maintenance of a strongly positive nitrogen balance. The proteins included in the diet were of good quality for serum protein regeneration, according to the recent work of Whipple and his coworkers[13] on the comparative efficiency of different dietary proteins. It was satisfactorily determined that extra protein was not lost by way of the urine, feces, or ascitic and edema fluids. Abnormal destruction of serum proteins appears to have been ruled out by the fact that the descent of their levels following blood transfusion was extremely slow. The second unusual point is the symmetrical reduction in the serum albumin and globulin fractions. At no time was the albumin-globulin ratio reversed. In fact, the regeneration of globulin appears to have been slightly more impaired than that of the albumin.

The characteristic lesion in the liver lobules was unique in that no true cirrhosis, no infiltration of wandering cells, and no necrotic cellular débris were apparent. Since the morphologic blood picture remained essentially normal and no other parenchymatous lesion than that in the liver was found, this observation appears to us to substantiate the theory of Whipple and coworkers[14a and b] that the liver is the chief site of formation of the serum proteins. The peculiar distribution of the lesions further suggests that this process may be a more or less specialized function of those cells situated in the intermediate and peripheral zones of the hepatic lobules.

The direct cause of the liver lesions is unknown. The early age of the patient at the onset of edema, the lack of any clear-cut history of preceding infection or intoxication and the small size of the hepatic cells might be interpreted as suggestive evidence of a congenital defect in the development of these structures, but no further proof of this somewhat fantastic explanation is available. It is of passing interest, however, that three years after the death of this patient, her parents brought a second child, eighteen months of age, to us with the complaint that she seemed at times to show slight edema similar to that shown by E. N. at the onset of her illness. No pitting edema could be demonstrated at the time of our examination, but her serum proteins as well as those of the parents were determined. From the point of view of heredity it may or may not be significant that this sister's total serum protein was

found to be but 6 per cent, and her father's but 6.12 per cent, while the mother's was 7.4 per cent. The parents were to report to us in case edema became apparent in this child. An additional year has passed, but no report has been received.

Various observers[15, 16, 17, 18] have reported a decrease in serum or plasma proteins in liver disease, particularly in cases of cirrhosis with ascites and edema. This has usually been attributed to underfeeding of protein in such cases, and the edema has often been referred to as being a result of cardiac insufficiency and venous obstruction. Myers and Keefer[18] found, however, that certain patients with severe cirrhosis lost significant amounts of protein into the ascitic fluid. They concluded that such patients probably suffer also from decreased ability to produce serum proteins, particularly albumin. They, like other contributors to the subject, found the albumin-globulin ratio of the serum to be reversed in the majority of instances. The case reported here and that reported by Myers and Taylor[2] differ from cases of ordinary cirrhosis in that there was never any tendency to a reversal. These two patients showed a marked deficiency in their capacity to fabricate globulin as well as albumin. This deficiency was the primary factor in their abnormal retention of water. The ascites was a feature of the generalized edema, just as it is in the case of lipoid nephrosis. There was no evidence of venous obstruction or of cardiac or renal insufficiency.

SUMMARY AND CONCLUSIONS

1. Clinical and metabolic studies were carried out over a period of many months in the case of a patient suffering from "idiopathic" hypoproteinemic edema.

2. No evidence of cardiac or renal disease was obtained during her lifetime. The formed elements of the blood were repeatedly found to be entirely normal.

3. The low levels of the serum albumin and globulin were uninfluenced by high protein feeding, although a strongly positive nitrogen balance was known to be maintained thereby over a period of more than six months.

4. Since no other cause for the symmetrical lowering of the serum proteins could be found, it was assumed that the body's mechanism for their regeneration was defective.

5. Studies on the water and mineral exchanges showed the edema per se to differ in no essential way from that due to the hypoproteinemia of protein starvation or that due to excessive protein loss.

6. Elevation of the serum proteins by means of blood transfusion resulted in complete disappearance of the edema, demonstrating a direct relationship between the low serum proteins and edema formation.

7. Postmortem examination revealed a comparatively widespread atrophy of hepatic cells, which was confined chiefly to the intermediate

and peripheral areas of the liver lobules, the central zone being spared. No lesions were present in the kidneys, heart, or other parenchymatous organs.

8. In the light of these data the tentative conclusion has been drawn that this unusual liver lesion was responsible for hypogenesis of the serum proteins and consequently for the development of edema and ascites.

9. Hypoproteinemia in the absence of albuminuria and protein starvation should be regarded as at least presumptive evidence of one form of hepatic insufficiency.

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TRAUMATIC PNEUMOTHORAX IN THE NEWBORN

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PNEUMOTHORAX is of uncommon occurrence in children. Scott[1] in 1928 collected 177 cases in children of various ages. In reporting his own case of pneumothorax, Davies[2] reviewed twenty-seven previously reported. In 1931 Coccheri and Rossi[3] reported 300 cases from the literature dating from 1844 to 1930, including sixteen cases of their own.

Stoloff[4] is of the opinion that tuberculosis is probably the most frequent single cause of pneumothorax in children. On the other hand, according to Anderson and Cathcart[5] tuberculosis as an etiologic factor is rare as compared to the 3 per cent occurrence in pulmonary tuberculosis in adults. However, in considering the nontuberculous causes of pneumothorax in infants and children, Lereboulet and his associates[6] and Royer de Véricourt[7] list pneumonia, empyema, lung abscess, and pertussis as the most frequent. Cases of spontaneous pneumothorax either accompanying or following pneumonia have been reported by Bashinski,[8] Lacchia,[9] Acuna and his coworkers[10] and others.[11, 12, 13] In reporting a case of pyopneumothorax from our service, Rogatz and Rosenberg[14] found only twelve similar cases in the literature occurring during the first year of life. Direct trauma to the chest (Macera and Perissé[15]) or prolonged difficult deliveries (Donahoe[16]) may also cause pneumothorax. Pissavy and Zimmer[17] report a case of pneumothorax following puncture of the pleura in a fifteen-year-old child. Ruge[18] in 1878 described the first case of pneumothorax in the newborn. In 1930 Stein,[19] in a report with a review of the literature, described four cases and added one of his own. Gasul and Singer[20] brought the series up to eight cases. In an excellent monograph, Glaser and Landau[21] reported seventeen cases, including one of their own, with a mortality of 47 per cent in pneumothorax in the newborn. Flipse[22] is the only author to report a case of pneumothorax following hypodermic medication. The following report of a case of pneumothorax in the newborn is of interest because we were unable to find in the literature a report of a similar case caused by attempted cardiac puncture.

From the Abraham Jacobi Division for Children of the Lenox Hill Hospital, New York, Service of Dr. Jerome S. Leopold.

CASE REPORT

(Courtesy of Dr. Arthur Stein)

H. P. H., male, newborn infant, was born by a precipitous delivery on Dec. 2, 1935, ten hours after the onset of labor. The birth weight was 5 pounds 8½ ounces.

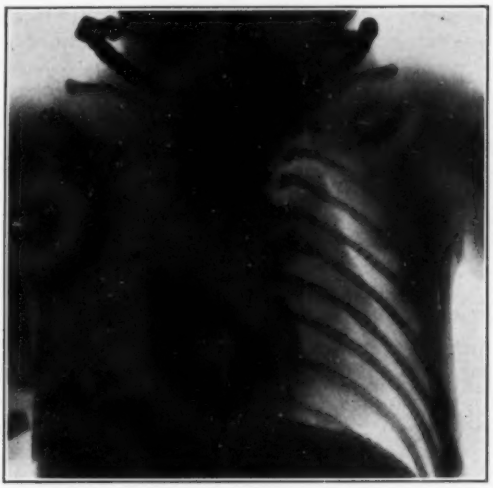

Fig. 1.—Showing a 50 per cent pneumothorax, partial collapse of the left lung, and shifting of the mediastinum to the right.

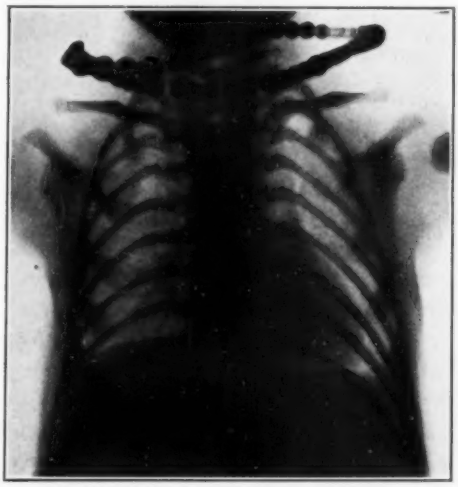

Fig. 2.—Showing complete absorption of the air, with the mediastinum normally located.

At birth the infant appeared very pale, listless, and did not breathe. In attempts at resuscitation, besides immersion in hot and cold water tubs, alternately, and dilatation of the rectum, one ampule of medication was injected supposedly into the heart

by means of a 24 gauge, ¾ inch needle. When a weak cry was heard, the infant was at once placed in an incubator and oxygen was administered continuously. Complete physical examination several hours later revealed the following findings:

The infant appeared apathetic and somewhat cyanosed. Stimulation produced a very weak cry. The respirations were rapid and shallow. The skin was pale and dry. The mucous membranes and the extremities were slightly cyanotic. The anterior fontanel was patent, of normal fullness, and admitted two fingers. The neck was normal. On the chest wall, a needle puncture wound was present in the third intercostal space, just to the left of the sternum. On the left side the thorax appeared fuller than on the right. The respiratory excursions were markedly diminished; tactile fremitus was practically absent; percussion produced a tympanitic note. The breath sounds were exaggerated over the entire right side, and were markedly diminished over the left chest. No râles were heard. The heart sounds were heard best to the right of the sternum. The abdomen was soft. The liver edge was easily palpated just below the right costal margin. The spleen was not felt. The genitals and extremities were negative. A diagnosis of left-sided pneumothorax was made and was confirmed by roentgen ray examination (Fig. 1). During the first thirty-six hours of life, the infant had four stools consisting of meconium and mucus streaked with fresh blood. The blood was explained on the basis of the trauma to the anus produced secondary to the dilatation procedure instituted as a stimulating measure at birth. The infant was kept in the incubator, and oxygen was administered continuously. The physical findings improved daily. It was noted that the point of maximum intensity of the heart sounds was steadily shifting from the right of the sternum to the left. The breath sounds on the left side gradually became normal.

On Dec. 9, 1935 (7 days after birth), the physical examination of the chest was entirely normal. Roentgen ray examination (Fig. 2) revealed complete disappearance of the pneumothorax. The oxygen was discontinued. The stools had become free of blood, and the infant was taking breast milk with a complementary formula satisfactorily. When discharged from the hospital on Dec. 11, 1935, the infant weighed 5 pounds 6½ ounces. When seen at the age of five months, he weighed 14½ pounds, was 25¾ inches long, and had two teeth. The infant was of normal development and well nourished.

DISCUSSION

In reviewing the literature on pneumothorax in the newborn, the explanation most frequently advanced for the mechanism of production is the rupture of an alveolus during resuscitation causing a bronchopleural fistula. Flipse[22] feels that forceful respiratory movements at the onset of respiration in his case were caused by an aplasia of the epiglottic cartilage with subsequent collapse obstructing the glottis. In Stein's[19] case there was apparently a permanent bronchial communication with the pleural cavity because at the end of two years no expansion of the right lung had occurred. In the case presented by Gasul and Singer,[20] the pathogenesis was described on the basis of aspiration of infected material at birth with the production of a localized pneumonitis. This process, going on to abscess formation, ruptured at the age of three weeks, causing pyopneumothorax and leading to death in three days. In the case reported by us, it is felt that

air entered the pleural cavity through the needle puncture wound during the first few respiratory efforts. With the onset of the respiratory movements and the subsequent production of a negative pressure in the pleural cavity, air was most likely sucked in through the puncture wound. This readily explains the rapid clearing up of the pneumothorax within seven days.

SUMMARY

A case of a newborn infant is presented in whom pneumothorax developed apparently secondary to puncture of the left chest. The air was spontaneously absorbed within seven days. Complete recovery resulted.

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THE BACTERIAL FLORA OF MECONIUM SPECIMENS COLLECTED FROM SIXTY-FOUR INFANTS WITHIN FOUR HOURS AFTER DELIVERY

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IN HIS dissertation of 1886 Escherich[1] stated that the meconium of the infant was sterile and bacteria did not appear until four hours after birth in the summer and seventeen hours in the winter. Subsequent workers, Schild,[2] Szego,[3] Sittler,[4] Tissier,[5] Cruickshank and Cruickshank,[6] and Passini,[7] furnished data supporting Escherich. Statements to this effect may be found in the texts of Ford,[8] Topley and Wilson,[9] Zinsser and Bayne-Jones,[10] Park and Williams,[11] and Kendall.[12]

Exceptions to these findings, however, have been recorded which suggest strongly that bacteria may occasionally be present in the meconium at birth. Hymanson and Hertz[13] found bacteria in nine of thirty-nine meconium specimens collected by rectal swab shortly after birth and streaked out on serum glucose agar. Burrage[14] in 1927 reported the cultivation on solid media of bacteria from thirty-eight of one hundred first passage specimens of meconium, the first of which was collected at delivery and was found to contain many bacteria. A similar series of fifty first passage specimens was recorded in 1934 by Hall and O'Toole[15] who obtained the same percentage of positive results as Burrage. They used both solid and liquid media. In the last two instances most of the specimens were obtained from sterile diapers brought to the laboratory from the nursery. No attempt was made to collect the specimens regularly at or within a short time of delivery.

The present investigation undertook to determine the presence of bacteria in the intestinal contents at birth, as well as in the four-hour period following delivery. The mode of invasion was also considered.

METHODS OF COLLECTION AND EXAMINATION

The time of collection ranged from four minutes to three hours and ten minutes after delivery. A swab on a fairly stiff copper or iron wire which was placed in a short length of glass tubing was used to collect the specimens. This combination, with a small amount of castor oil for lubrication, was placed in a test tube and sterilized in the autoclave at fifteen pounds' pressure for one-half hour. Several tests showed the oil to be sterile. The anal region of each of the first few infants was sponged with Sharpe and Dohme S. T. 37, but this was

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discontinued because of its slow evaporation and 95 per cent alcohol was used for the remaining cases. A control test of this area was made by rubbing it with an ordinary swab which was placed in glucose broth. These control cultures showed that this method of sterilizing the anus and buttocks was not entirely efficacious, but no other satisfactory method was found. The meconium was collected by inserting the tube well past the anal sphincter, pushing the swab still farther into the rectum, and withdrawing the swab, which brought meconium into the tube.

The following technic was employed for examining the meconium. When the meconium was present in sufficient quantity, it was examined microscopically by cover slip as well as Gram's stain. The results of these examinations were invariably negative. A small amount of meconium was streaked across eosin methylene blue and blood agar plates to determine the presence of gram-negative and gram-positive aerobic organisms, respectively. An additional amount was placed in freshly boiled and cooled brain medium for the enrichment of what few bacteria might be present whether aerobic or anaerobic. In a few cases when brain broth was not available glucose broth was used. Occasionally the meconium was streaked out on blood agar slants which were made anaerobic under alkaline pyrogallol; these were all sterile.

RESULTS

To date, the meconium collected by this method within four hours after delivery was examined from sixty-four infants, including two of cesarean birth. These cases were divided in respect to time as follows: twenty-nine were collected within thirty minutes after delivery; ten between thirty minutes and one hour; sixteen between one and two hours; and nine between two hours and three hours and ten minutes.

The thirty-minute period was selected arbitrarily to cover as many cases as possible within a short time after the arrival of the baby. The babies who came within this limit, the organisms isolated, and the control cultures of the skin surface of the anal area are listed in Table I.

Table I shows that three out of twenty-nine specimens of meconium obtained within thirty minutes after delivery showed positive bacterial growth on streaked plates. That these organisms must have been present at birth in Case 6 seems indisputable, for the specimen was collected nine minutes after delivery, and there were numerous colonies along the streak on the blood agar plate. The failure of the *L. acidophilus* to grow in enrichment media cannot be explained. In Case 29, colonies appeared in large numbers along the streak on the blood agar plates. Among these were hemolytic colonies of *Streptococcus pyogenes* whose presence in a meconium specimen collected within a half-hour after delivery caused some concern for the mother, but nothing abnormal was recorded for the postpartum period of ten days in the hospital.

Str. mitis was also isolated from the plate, and both species of streptococcus and *B. coli* were recovered from the enrichment culture. In Case 27 there were only three colonies of *B. coli* at the beginning of

TABLE I

BACTERIAL FLORA OF SPECIMENS OF MECONIUM COLLECTED WITHIN THIRTY MINUTES AFTER DELIVERY

NO.	TIME*	RESULTS		
		PLATE	ENRICHMENT	SKIN CULTURES
1	4	Sterile	Sterile	Sterile
2	8	Sterile	Sterile	Sterile
3	8	Sterile	Sterile	Sterile
4	8	Sterile	Sterile	*B. coli*
5	9	Sterile	Sterile	*M. epidermidis*
6	9	*L. acidophilus*	Sterile	Sterile
7	10	Sterile	Sterile	Sterile
8	10	Sterile	Sterile	Sterile
9	10	Sterile	Sterile	Sterile
10	10	Sterile	Sterile	Sterile
11	10	Sterile	Sterile	Sterile
12	11	Sterile	Sterile	Sterile
13	11	Sterile	Sterile	Sterile
14	13	Sterile	*B. coli*	*B. coli*
15	13	Sterile	Bacteroides species	*M. epidermidis*
16	14	Sterile	Sterile	Sterile
17	14	Sterile	Sterile	Sterile
18	15	Sterile	Sterile	Sterile
19	15	Sterile	Bacteroides species	Sterile
20	16	Sterile	Sterile	Sterile
21	16	Sterile	*M. aurantiacus*	*M. epidermidis*
22	17	Sterile	Sterile	Sterile
23	18	Sterile	Sterile	Sterile
24	19	Sterile	Sterile	*Str. mitis*
25	20	Sterile	Sterile	Sterile
26	20	Sterile	Anaerobic coccus	Sterile
27	20	*B. coli*	*B. coli* *Str. fecalis*	*B. coli* *Str. fecalis*
28	26	Sterile	Sterile	Sterile
29	30	*Str. pyogenes* *Str. mitis*	*Str. pyogenes* *Str. mitis* *B. coli*	Not taken

*Time in minutes from birth to collection of specimen.

TABLE II

SPECIMENS OF MECONIUM COLLECTED BETWEEN THIRTY AND SIXTY MINUTES AFTER DELIVERY

NO.	TIME BETWEEN DELIVERY AND COLLECTION	RESULTS		
		PLATE	ENRICHMENT	SKIN CULTURES
1	31*	Sterile	Sterile	Sterile
2	34	Sterile	Sterile	Sterile
3	35	Sterile	*L. acidophilus*	*M. epidermidis*
4	39*	Sterile	Sterile	Sterile
5	52	Sterile	Sterile	Sterile
6	55	Sterile	Sterile	Sterile
7	57	Sterile	Sterile	Sterile
8	59	Sterile	*B. coli*	Sterile
9	59	Sterile	*M. epidermidis*	Sterile
10	59	Sterile	*B. coli* *C. hofmanni*	Sterile

*Cesarean birth.

the streak, but *B. coli* and *Str. fecalis* were isolated from the enrichment cultures as well as the skin area. Bacteria were demonstrated in five more of the specimens by enrichment procedures. The isolation of the unidentified species of the genus Bacteroides and the anaerobic coccus indicates the necessity for anaerobic methods in this type of study. The relation of the organisms isolated from the meconium and skin areas by enrichment is discussed later.

Specimens of meconium were collected from ten babies between thirty and sixty minutes after delivery; the results are summarized in Table II.

In the small series listed in Table II no bacteria were isolated directly, but in four of the ten specimens bacteria were shown to be present by enrichment methods. Only one control culture from the skin was positive for bacterial growth, and no duplication occurred with the corresponding culture of meconium in enrichment medium.

Sixteen specimens of meconium were collected between one and two hours after delivery; the results are recorded in Table III.

TABLE III

SPECIMENS OF MECONIUM COLLECTED BETWEEN ONE AND TWO HOURS AFTER DELIVERY

NO.	TIME BETWEEN BIRTH AND COLLECTION	RESULTS		
		PLATE	ENRICHMENT	SKIN CULTURES
1	1:00	Sterile	*C. hofmanni*	Sterile
2	1:00	Sterile	*M. albus*	*M. epidermidis*
3	1:03	Sterile	*M. candidus* *D. catarrhalis*	Sterile
4	1:04	Sterile	*L. acidophilus*	Not taken
5	1:05	Sterile	*B. coli*	Sterile
6	1:10	Sterile	Sterile	Sterile
7	1:15	Sterile	*B. welchii* *C. hofmanni* *M. epidermidis*	Sterile
8	1:15	Sterile	Sterile	Hay bacillus
9	1:15	Sterile	Sterile	Not taken
10	1:16	Sterile	Sterile	Sterile
11	1:21	Sterile	*M. epidermidis* *S. salivarius*	*M. epidermidis*
12	1:30	Sterile	*B. coli* *M. epidermidis*	Sterile
13	1:43	Sterile	Sterile	*M. epidermidis* *Str. salivarius*
14	1:46	Sterile	Sterile	Sterile
15	1:53*	Sterile	*Str. fecalis* *B. coli*	Sterile
16	1:56*	Sterile	*Str. fecalis* *B. coli*	Sterile

*Twins.

No bacteria were demonstrated by direct plating in any of the sixteen meconium specimens recorded in Table III. With enrichment media, however, ten of the sixteen specimens yielded positive results. This is a distinct increase in the positive results over those obtained

in the preceding time periods. The isolation of *B. welchii,* the one species of sporulating anaerobe encountered, indicates again the necessity of anaerobic methods.

Nine specimens were obtained between two hours and three hours and ten minutes after delivery. These are shown in Table IV.

TABLE IV

BACTERIAL FLORA OF SPECIMENS OF MECONIUM COLLECTED BETWEEN TWO HOURS AND THREE HOURS AND TEN MINUTES AFTER DELIVERY

NO.	TIME BETWEEN BIRTH AND COLLECTION	RESULTS		
		PLATE	ENRICHMENT	SKIN CULTURES
1	2:00	Sterile	*M. aurantiacus*	Sterile
2	2:05	Sterile	Sterile	Sterile
3	2:17	Sterile	*Str. salivarius*	Not taken
4	2:25	Sterile	*M. epidermidis*	Sterile
5	2:35	Sterile	*M. albus*	*M. albus*
6	2:46	Sterile	*M. epidermidis*	Not taken
7	3:00	*L. acidophilus*	*M. candidus* *L. acidophilus*	Not taken
8	3:03	Sterile	*M. candidus*	Sterile
9	3:10	Sterile	Sterile	Sterile

Table IV shows that in only one case were bacteria numerous enough to be demonstrated by direct plating, but nine of the ten specimens gave positive results with enrichment methods. Only one of seven control cultures from the skin was positive for bacterial growth; the same species, *M. albus,* was also isolated by enrichment from the corresponding meconium specimen.

The species isolated from the specimens of meconium from sixty-four newborn infants within four hours after delivery are summarized in Table V in respect to frequence, time intervals, and methods of isolation. The cultures from the skin tests are included for comparison.

Table V shows that only four species of bacteria were isolated by direct plating methods. These species included two strains of *L. acidophilus* and one each of *B. coli, Str. pyogenes,* and *Str. mitis.* Thirteen known species, two unidentified species of the genus Bacteroides, and one unidentified anaerobic coccus were isolated by enrichment methods. Their frequence is given: *B. coli,* nine times; *M. epidermidis,* six; *L. acidophilus,* four; *C. hofmanni, Str. fecalis,* and *M. candidus,* three; *M. albus, M. aurantiacus, Str. salivarius, D. catarrhalis,* and Bacteroides species, two; and *Str. pyogenes, Str. mitis, B. welchii,* and an unidentified anaerobic coccus, once each.

The bacteria recovered from the skin cultures were six strains of *M. epidermidis,* three of *B. coli,* and one each of *Str. mitis,* hay bacillus, *Str. fecalis,* and *M. albus.*

DISCUSSION

Although specimens of meconium were obtained up to three hours and ten minutes after delivery, it was obvious that those collected as soon

TABLE V

FREQUENCY OF BACTERIAL SPECIES IN SPECIMENS OF MECONIUM COLLECTED WITHIN FOUR HOURS AFTER DELIVERY

	METHODS														
	DIRECT PLATING					ENRICHMENT					SKIN CULTURES				
	0-30 MIN.	30 MIN.-1 HR.	1-2 HR.	2-4 HR.	TOTAL	0-30 MIN.	30 MIN.-1 HR.	1-2 HR.	2-4 HR.	TOTAL	0-30 MIN.	30 MIN.-1 HR.	1-2 HR.	2-4 HR.	TOTAL
B. coli	1				1	2	3	4		9	3				3
M. epidermidis							1	3	2	6	2	1	3		6
C. hofmanni							1	2		3					
L. acidophilus	1			1	2		1	1	1	3					
M. candidus								1	2	3					
M. albus								1	1	2				1	1
Str. salivarius								1	1	2			1		1
Str. fecalis						1		2		3	1				1
M. aurantiacus						1			1	2					
D. catarrhalis								1	1	2					
Bacteroides species						2				2					
Str. pyogenes	1				1	1				1					
Str. mitis	1				1	1				1	1				1
B. welchii								1		1					
Anaerobic coccus							1			1					
Hay bacillus													1		1
Specimens	29	10	16	9	64	29	10	16	9	64	26	9	14	6	55
Negative	26	10	16	8	60	22	6	6	2	36	19	8	10	5	42
Positive	3	0	0	1	4	7	4	10	7	28	7	1	4	1	13
% Positive	10.4			11.1	6.3	24.1	40.0	62.5	78.0	48.3	24.6	12.5	28.0	16.7	23.6

as possible were of more value in answering the question whether bacteria are present in the meconium at birth. The most striking proof was the specific case where the collection was made nine minutes after delivery. Nothing had been done to the infant, such as washing or taking the rectal temperature. No organisms were isolated from the skin of the anal region by enrichment, but numerous delicate colonies appeared in from forty-eight to seventy-two hours along the streak on the blood agar plate inoculated with the meconium. These organisms were tentatively classified as Doederlein's bacillus or *L. acidophilus*, the identity of which was pointed out by Thomas[16] in 1928. The presence of such numbers of bacteria, even if not seen microscopically, would seem to be proof of their multiplication in the meconium before birth.

The relation of the bacteria isolated from the skin surface of the anal areas to those recovered from the meconium by enrichment methods warrants some consideration because it would seem that the isolation of organisms from the anal area might limit the value of the positive results obtained by enrichment of the respective meconium specimens. Three possibilities exist: First, when bacteria are isolated from the meconium and not from the anal area, it would indicate the presence of a few organisms in the meconium and either that cleansing of the skin of the anal region was satisfactory or that the surface was sterile at birth. Second, the culturing of bacteria from the skin and not the meconium suggests that although the cleansing was not completely efficient, organisms had not invaded the meconium. Third, isolation of the organisms from both skin and meconium may be interpreted in two ways. The isolation of a species from the anal area unlike the species recovered from the meconium would not necessarily interfere with the assumption of bacterial growth from a few cells in the meconium. The isolation of the same species from both skin area and meconium, however, suggests either the occurrence of per anum invasion with natural duplication of results from these two sources or direct exterior contamination of the meconium specimen from the skin.

If the thirteen cases of positive skin cultures are analyzed in light of these possibilities, it is found that in five cases bacteria were recovered from the anal areas only, in four cases different species were isolated from anal areas and the corresponding meconium specimens, and in only four cases were the species from the two sources identical. Therefore, it would appear that only the last four cases should be eliminated on the ground of exterior contamination. In addition, there were six cases in which no skin cultures were made. One was sterile, one had hemolytic streptococci in the meconium as demonstrated by direct plating, and the other four were positive for bacteria by enriching methods. If the four cases of duplication and the four positive cases with no skin cultures be eliminated from the series, there remain fifty-six specimens of meconium from the series, in twenty of which bacteria were demonstrated

by enrichment methods. These results indicate the presence of only a few bacterial cells, except possibly the cases from which anaerobes were isolated, in the meconium.

In this series the percentage of positive results with solid media was only 6.3 per cent, which is much lower than the 23 per cent reported by Hymanson and Hertz,[13] the 38 per cent by Burrage,[14] and the 30 per cent by Hall and O'Toole.[15] Enrichment results gave 35.7 per cent, a figure which is not significantly different from the 38 per cent obtained by Hall and O'Toole with both solid and enrichment media. It is possible that some of the discrepancies may be explained by the failure of Hymanson and Hertz to cleanse the skin of the anal area before the specimen was collected, and that Burrage, Hall and O'Toole limited their studies to first passage specimens. Hall and O'Toole reported specimens microscopically positive which were collected thirteen, twenty-six, and seventeen hours, respectively, after birth which findings led Hall (personal communication) to believe that postnatal bacterial invasion accounted for many of the positive results in the study of first passage meconium specimens. The present investigation was designed to cover these points and to get the specimens within a short period after delivery under aseptic precautions, and it would seem that the positive cases reported furnish reliable evidence that bacteria are present in the meconium at birth in a small percentage of cases. Thus the essential point in this investigation is not that the solid media results are so greatly different or that the enrichment results approximate the figures given previously, but that the meconium is not always sterile at birth.

To explain the presence of bacteria in the meconium of newborn infants in numbers to be demonstrated by plating or enrichment media, if contamination can be ruled out, three routes of infection may be considered. First, it is possible that bacteria invade the meconium during passage of the fetus through the birth canal, but the natural process of delivery prevents any serious investigation. Second, the bacteria may have been deposited in the intestine from the blood stream. In this study no attempt was made to run control tests on the blood of the mother and child. Third and most plausible, the amniotic fluid may have been infected by the organisms of the vaginal flora. Since the fetus is surrounded by amniotic fluid, which enters the intestinal tract, as evidenced by the presence of lanugo hair, epidermal cells, and vernix caseosa in the meconium,[17] it would not be unreasonable to expect bacterial invasion of the meconium if the fluid became infected. Therefore, a relation should exist between the time of rupture of the fetal membranes and birth with the appearance of bacteria in the meconium; that is, the longer the time between fetal membrane rupture and delivery, the greater should be the chance of finding bacteria in the intestinal tract. A similar relation of time between rupture and inflammation of the fetal membranes and congenital pneumonia in stillborn and newborn

infants dying in the first three days was pointed out by Johnson and Meyer.[18] Hall and O'Toole,[15] however, could not show that time elapsing from rupture of the fetal membranes to birth influenced the presence of bacteria in fifty first passage meconium specimens. Similarly, in the present study little or no relation could be established between the time from fetal membrane rupture to delivery, inflammation in the membranes, and the presence of bacteria in the meconium of fifty of the sixty-four cases studied.

SUMMARY

In three of twenty-nine specimens of meconium collected within thirty minutes after delivery, bacteria were demonstrated by plating methods. These three positive cases indicate that prenatal bacterial invasion of the intestinal tract does occur in a small percentage of cases.

Some of the positive results obtained by enrichment might be invalidated by the failure to sterilize thoroughly the skin surrounding the anus, but a large number with corresponding sterile skin cultures, or skin cultures showing other bacterial species than in the meconium, indicated that a few organisms were present in the meconium at birth in about 36 per cent of this series of sixty-four specimens.

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THE BACTERIAL FLORA OF THE INTESTINAL CONTENTS OF TWENTY-SEVEN STILLBORN INFANTS

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IT WAS shown in a preceding study of newborn infants that bacteria could be demonstrated by plating methods in three of twenty-nine specimens of meconium collected within thirty minutes after delivery.[1] These findings indicated that bacteria were present in the intestinal tracts of infants at birth in a small percentage of cases. In order to study further the occurrence of bacteria in the intestinal tract at birth, segments of the intestines of twenty-seven stillborn* babies were examined.

Despite the large amount of work recorded on the sterility of the meconium at birth and the bacterial invasion of normal living infants, only two references dealing directly with intestinal examinations of stillborn material were found in the available literature. Both Escherich,[2] who examined three stillborn infants, and Popoff,[3] who killed newborn kittens and puppies, were unable to demonstrate bacteria in any of these and concluded that the fetal meconium was sterile at birth.

METHODS OF COLLECTION AND EXAMINATION

In the first fifteen cases only one segment was taken from the intestinal tract. This was from the ascending colon as close as possible to the cecum, and was selected because it was thought to be least exposed to either oral or anal bacterial invasion. Therefore, if bacteria were found, it would seem indisputable evidence that bacteria were present in the intestinal tract at birth. In the remaining twelve cases segments were taken from the descending colon, ascending colon, ileum, and duodenum. The segments were tied off, cut, and placed in sterile Petri dishes, and in the first fifteen cases they were dipped momentarily in boiling water. Those from the other twelve were seared with a hot spatula. The sections were opened with instruments that had been boiled or flamed. Smears of the contents were stained by Gram's method and were negative except in one case where large gram-positive rods were observed. The contents were also streaked across eosin methylene blue and blood agar plates and were placed in freshly boiled and cooled deep brain medium.

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*No distinction is made between the terms "stillborn" and "deadborn."

RESULTS

The fifteen infants from whom only one section of the intestine was taken are recorded in Table I in the order of the time elapsing between death and autopsy.

Table I shows there is apparently little relationship between the time of delivery and autopsy and the presence of bacteria in the intestines

TABLE I

BACTERIAL FLORA OF THE INTESTINAL CONTENTS AT THE ASCENDING COLON OF 15 STILLBORN INFANTS

NO.	HOURS*	SECTION	RESULTS	
			PLATES	ENRICHMENT
1	3	Ascending colon	Sterile	Sterile
2	14	Ascending colon	Sterile	Sterile
3	18½	Ascending colon	Sterile	Sterile
4	27	Ascending colon	Sterile	Sterile
5	30	Ascending colon	Sterile	Sterile
6	30	Ascending colon	Sterile	Sterile
7	57	Ascending colon	Sterile	Sterile
8	63	Ascending colon	Sterile	Sterile
9	66	Ascending colon	Sterile	Sterile
10	66	Ascending colon	Sterile	Sterile
11	72	Ascending colon	Sterile	*M. aureus*
12	73	Ascending colon	Sterile	Sterile
13	109	Ascending colon	Sterile	*M. epidermidis*
14	?	Ascending colon	Sterile	Sterile
15	?	Ascending colon	Sterile	Sterile

*Time in hours between delivery and autopsy.

of stillborn infants. In only two of the fifteen cases were bacteria demonstrated, and in both of these only after enrichment. These cases are discussed in detail as follows:

CASE 11.—No clinical history was available for this premature infant, who weighed about 5 pounds. Autopsy revealed extensive subarachnoidal hemorrhage. Other sites of hemorrhage were in the pleurae, epicardium, scalp, tentorium cerebelli, and falx cerebri. The heart's blood was sterile. *M. aureus* was isolated by enrichment from the ascending colon. Time of the rupture of the fetal membranes and the condition of the membranes and placenta were unknown.

CASE 13.—This premature infant of about six months' gestation was apparently dead from the nephritic toxemia of the mother. Autopsy showed slight maceration, petechial hemorrhages in the thymus, parietal pericardium, epicardium, scalp, and epicranium, and slight congestion of the cerebrum. The membranes ruptured eighteen and one-half hours before delivery and were acutely inflamed. The heart's blood was sterile. *M. epidermidis* was isolated from the ascending colon by enrichment. The mother made an uneventful recovery.

The significance of the positive enrichment cultures will be considered in the discussion.

The bacteriologic study of the sections taken from various portions of the intestinal tract of twelve stillborn infants is given in Table II.

In contrast to the first series, the data presented in Table II show that the intestinal contents of only one of twelve stillborns to be sterile in

TABLE II

BACTERIAL FLORA OF THE CONTENTS OF VARIOUS PORTIONS OF THE INTESTINAL TRACT OF STILLBORN INFANTS

NO.	TIME HOURS*	DUODENUM	ILEUM	ASCENDING COLON	DESCENDING COLON
16	14	Sterile	Sterile	Sterile	*M. epidermidis* *Str. fecalis*
17	16¾	*B. welchii*†	*B. welchii*†	*B. welchii*†	*B. welchii*†
18	22	Sterile	Sterile	Sterile	*M. citreus* *Str. nonhemolyticus II*
19	23	Sterile	Sterile	Sterile	Sterile
20	24	Sterile	Sterile	Sterile	*B. alkaligenes*‡ *M. flavus*‡ *Str. ignavus*‡
21	24	*B. alkaligenes*‡	Sterile	Sterile	*M. citreus* *B. coli*
22	24	Sterile	Sterile	*M. aurantiacus*	*B. coli*
23	28¾	*B. tertius*	Sterile	Sterile	Sterile
24	30	Sterile	Sterile	Sterile	*B. coli* *Sarcina lutea*
25	30	Sterile	*M. luteus*‡	*M. luteus*‡	*M. luteus*‡
26	50	*C. hofmanni*‡	Sterile	Sterile	Sterile
27	53	Sterile	Sterile	Sterile	*M. varians*‡

*Time in hours between delivery and autopsy.
†Observed microscopically in contents.
‡Isolated by direct plating.

sections taken from the duodenum, ileum, ascending colon, and descending colon. Bacteria were isolated by direct plating and enrichment methods in the other eleven cases. These cases are reported as follows:

CASE 16.—This was a full-term infant, weighing about 9 pounds, anatomically normal. The heart's blood was sterile. *M. epidermidis* and *Str. fecalis* were isolated by enrichment from the descending colon.

The mother had a massive hemorrhage from a duodenal ulcer before she was brought to the hospital on the evening before delivery. Fetal movements could not be discerned at the time of entrance. Death of the baby was believed to be due to the anemia of the placenta which resulted from the hemorrhage; the placenta and membranes were free from inflammation.

CASE 17.—The body was that of a full-term child who weighed about 8 pounds. The delivery was a breech presentation, and apparently the head was retained in the cervix until death occurred. The placenta, the membranes, and the cord were acutely inflamed. Autopsy showed atelectasis, slight bilateral tentorial tears with no hemorrhage, and aspiration of amniotic fluid. Large gram-positive rods were observed microscopically in the duodenum, the ileum, the ascending colon and the descending colon. These were isolated and identified as *B. welchii*. Since the child was born in this hospital and remained most of the sixteen and three-fourth hours from birth to autopsy in the ice box, it would seem that the presence of organisms in sufficient number to be demonstrated microscopically would be clear-cut evidence that the bacteria invaded and multiplied in the meconium before birth.

CASE 18.—This full-term, 8-pound infant was delivered by version and extraction after a shoulder presentation was determined. The cord was not pulsating before the patient was taken to the delivery room. The placenta was normal; no information was available about the rupture of the membranes. Autopsy revealed a broken neck

and atelectasis. The heart's blood was sterile. The inoculated plates were negative, but *M. citreus* and *Str. nonhemolyticus II* were isolated by enrichment from the descending colon.

CASE 20.—The clinical history furnished no definite reason for the death of this 6½-pound full-term infant. The doctor who delivered this case in an outside institution reported a velamentous insertion of the cord with rupture of the membranes adjacent to the site of insertion, but there was no record of hemorrhage. The gross pathology was limited to atelectasis. *B. alkaligenes, M. flavus,* and *Str. ignavus* were isolated by both plating and enrichment from the descending colon.

CASE 21.—This was a premature infant of about the seventh lunar month of gestation, weighing about 3 pounds. It was brought in from another hospital, and no information was secured about the clinical history. Autopsy showed pneumothorax. *B. alkaligenes* was isolated by both plating and enrichment methods from the duodenum; *M. citreus* and *B. coli* were isolated by enrichment from the descending colon.

CASE 22.—This was a full-term infant who was delivered in another hospital. The mother's labor was prolonged. Forceps were applied unsuccessfully and with heavy laceration which apparently caused the death of the baby. The body had already been opened. No heart's blood was taken, but *M. aurantiacus* was isolated from the ascending colon by enrichment, and *B. coli* was recovered from the descending colon after enriching of the contents.

CASE 23.—This infant was about one month premature, and weighed about 5 pounds. The heart was beating at birth, but no respirations were made. The delivery was a footling presentation, and great difficulty was encountered in removing the head. Membranes ruptured about one and a quarter hours before delivery; the placenta was normal. The heart's blood was sterile. Tentorial tears with resultant hemorrhage were found at autopsy. *B. tertius* was recovered by enrichment from the duodenum. All other cultures were sterile.

CASE 24.—The body was that of a full-term infant weighing 8½ pounds. It was born in an outside institution, and no clinical history was available. Autopsy showed tentorial tears with hemorrhage. The heart's blood was sterile. *Sarcina lutea* and *B. coli* were isolated by enrichment from the descending colon.

CASE 25.—This was a full-term infant whose heart was beating up to twelve hours before delivery but was not beating at birth. There was no apparent clinical cause for death. Autopsy showed moderate congestion of the lungs and some "congenital pneumonia." The heart's blood was sterile. The membranes were moderately inflamed, having ruptured thirty hours before delivery. *M. luteus* was isolated directly by plating methods from the ileum, the ascending colon and the descending colon.

CASE 26.—This full-term infant was delivered after a breech presentation. The heart was beating, but the infant made no attempt to breathe. Resuscitation was abandoned after forty-five minutes. Autopsy showed fetal atelectasis and tentorial tears. The membranes ruptured two hours before delivery; neither placenta, membranes, nor cord was inflamed. The heart's blood was sterile. From the white mucoid material of the jejunum, which was microscopically negative, *C. hofmanni* was isolated by direct plating. The other sections were sterile.

CASE 27.—This infant was slightly premature and was delivered dead after a breech presentation. Autopsy showed fetal atelectasis and a patent intraventricular

septum. The heart's blood was sterile. Three colonies of *M. varians* were found at the beginning of the streak on blood agar, and this species was also isolated by enrichment. All positive cultures were obtained from the descending colon.

If the study is analyzed in respect to the intestinal segments studied rather than according to the case, it is noted that four of the twelve duodenal specimens yielded bacteria, and in three of the four cases organisms were demonstrated by plating methods or microscopically. Only two ileal segments were positive but one showed bacterial cells when examined microscopically. Bacteria were demonstrated three times by plating and enrichment in the ascending colon sections and once microscopically. Nine of the twelve descending colon segments showed bacteria to be present by plating or enrichment methods, and one, microscopically. This might indicate a more frequent per anum bacterial invasion of the intestine than per os.

Sixteen species were isolated from the intestinal contents of the twenty-seven stillborn infants. Their frequence is given as follows: *B. coli, B. alkaligenes,* and *M. citreus,* three times; *M. epidermidis,* two times; and *M. flavus, M. luteus, M. varians, M. aureus, M. aurantiacus, Str. ignavus, Str. fecalis, Str. nonhemolyticus II, C. hofmanni, B. welchii, B. tertius,* and *Sarcina lutea,* once each.

DISCUSSION

Proof for prenatal bacterial invasion of the intestinal tract in stillborn as with newborn infants depends entirely upon microscopic and cultural examination of the intestinal contents. The presence of organisms in the intestinal contents of a stillborn child as demonstrated by the microscope soon after birth would seem to furnish absolute proof that bacteria may be present at or before birth. The observation of gram-positive rods similar to *B. welchii,* which was subsequently isolated, in Case 17, is offered as the most suggestive evidence in this series. Next in value to microscopic proof is the culturing of organisms directly on solid media so that the position and number of the resultant colonies cannot be mistaken for contamination. This condition occurred in Cases 20, 21, 25, and 26. Positive enrichment cultures are least valuable because growth in liquid media may result from either too few organisms to be demonstrated by plating methods or from exterior contamination. Although there was no skin sterilizing factor in this study, the surfaces of the segments had to be cleansed. This was accomplished by either dipping momentarily into boiling water or searing with a spatula. The segments were opened with either freshly boiled or flamed scissors and forceps. Despite these precautions the isolation of such organisms as *Sarcina lutea* would lead one to doubt the validity of positive enrichment results in all cases. This leaves the obvious conclusion that reliable data are best obtained with solid media and positive microscopic evidence.

Three possible methods for prenatal invasion of the intestinal tracts of stillborn infants are to be considered: (1) neonatal septicemia, (2) infection of the amniotic fluid, and (3) during passage of the fetus through the birth canal.

A possible relation exists between the septicemias of the stillborn and the organisms found in the intestinal tracts of these cases. Some cases of neonatal septicemias have been described in detail by Slemons,[4] DeLee,[5] and Serbin.[6] In the present series only two of twenty-one cases gave positive blood cultures at autopsy, and the organisms isolated, *M. tetragenus* and *Bact. pyocyaneum*, respectively, were not recovered from the intestine in any case studied. Therefore, it may be said that there was no correlation between the organisms isolated from the heart's blood and those isolated from the intestinal tract in this group of stillborn infants.

The early rupture of the fetal membranes with subsequent infection of the amniotic fluid by the vaginal organisms and invasion of the intestinal tract of the fetus either per os or per anum or both offers the most plausible method of infection. The somewhat analogous rôle between early rupture of the fetal membranes and congenital pneumonias in the newborn and stillborn was pointed out by Johnson and Meyer.[7] However, Hall and O'Toole[8] could not establish any relation between the time elapsing between the rupture of the fetal membranes and the presence of bacteria in the first passage of meconium. In the preceding study of a series of sixty-four specimens of meconium from newborn infants collected within four hours after delivery,[1] this relationship could not be determined. It seemed important, nevertheless, to compare the stillborn with the normal newborn in this respect. It was difficult to secure accurate information about the rupture of the fetal membranes; the available data, however, are listed in order of increasing time from rupture to delivery, and the histologic examination of the placentas in these and other cases is also included in Table III.

Too few cases are included in Table III to establish any definite relation between the time elapsing between rupture of the fetal membranes and delivery, the condition of the membranes, and bacteria in the intestinal contents of stillborn infants. It does seem significant, however, that in four of the five cases showing moderate to acute inflammation of the fetal membranes, bacteria were isolated from the intestinal contents. On the other hand, *C. hofmanni* was isolated directly in large numbers from Case 5 in which the membranes ruptured allegedly forty-five minutes before delivery and the fetal membranes showed no sign of inflammation, and in Case 13 the fetal membranes were acutely inflamed, but no bacteria were isolated from the intestinal contents.

This problem is confused by the inability to collect accurate information about the rupture of the membranes because so-called "high" ruptures may pass unnoticed but permit invasion of the amniotic fluid by

TABLE III

RELATION BETWEEN THE TIME OF RUPTURE OF THE FETAL MEMBRANES TO DELIVERY, INFLAMMATION OF THE MEMBRANES, AND THE PRESENCE OF BACTERIA IN THE INTESTINAL CONTENTS OF STILLBORN INFANTS

NO.	TIME IN HOURS*	CONDITION OF FETAL MEMBRANES	BACTERIAL FLORA OF THE INTESTINAL CONTENT
1	At birth	Normal	Sterile
2	At birth	Normal	Sterile
3	At birth	Normal	Sterile
4	At birth	Normal	Sterile
5	0:45	Normal	*C. hofmanni*†
6	4:45	Normal	Sterile
7	14:30	Normal	Sterile
8	15:45	Normal	Sterile
9	17:00	Acute inflammation	*B. welchii*‡
10	18:45	Acute inflammation	*M. epidermidis*
11	30:00	Moderate inflammation	*M. luteus*†
12	?	Acute inflammation	*M. aureus*
13	?	Acute inflammation	Sterile
14	?	Normal	Sterile
15	?	Normal	Sterile
16	?	Normal	Sterile
17	?	Normal	*M. citreus* *Str. nonhemolyticus II*

*Time in hours from rupture to delivery.
†Isolated by plating.
‡Observed microscopically.

the vaginal flora. After membrane rupture some time must elapse before bacteria can multiply in the amniotic fluid, and then the fetus may or may not swallow the infected fluid. The same possibility exists for the invasion by bacteria per anum. The fetus may be delivered before inflammation of the membranes occurs and still have bacteria in the intestinal tract. Finally, the hygiene of the individual mother frequently determines the number and type of organisms in the vaginal tract[9]; that is, the flora ranges from a homogenous but scanty flora of gram-positive rods, Doederlein's bacillus or *L. acidophilus*,[10] with a highly acid secretion (Grade I) to a mixed flora with a more alkaline secretion (Grade III). Thus it is probable that the type of vaginal flora determines the amount of infection of the amniotic fluid and in turn the organism isolated from the intestine of the newborn and the stillborn infant.

The remaining possible route of prenatal infection of the intestinal tract is during the passage of the fetus through the birth canal. As in the newborn series this mode of invasion could not be studied seriously.

SUMMARY

The presence of *B. welchii* microscopically and culturally in the duodenum, the ileum, the ascending colon and the descending colon of a stillborn infant is considered as reliable evidence that bacteria may invade the intestinal tract of the infant before or during birth. Additional evidence of slightly less value was obtained by finding numerous

colonies along the streaks on plates inoculated from the intestinal contents of four stillborn infants. The results obtained by enrichment were regarded as of doubtful significance because of the possibility of accidental contamination, except in the one case where *B. welchii* was isolated after being observed microscopically.

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ACTIVE ARTIFICIAL IMMUNIZATION IN DIPHTHERIA

The Relative Effectiveness of Various Antigens and the Duration of Immunity

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ALTHOUGH the value of diphtheria immunization is unquestioned, there is still some uncertainty about the best method of producing it; i.e., the method which will result regularly in the maximum percentage of immune subjects with a minimum of injections and unpleasant reactions. Certainly, effectiveness and simplification are the two primary requisites for any method of immunization advised on a large scale. The high incidence of susceptibility in children, especially those in the preschool age, has led to the general acceptance of the view that preliminary Schick tests in children should be omitted and that every child should be immunized. Another advance in simplification of the general procedure will be made when a method of immunization can be shown to result regularly in such a high percentage of immunes that subsequent Schick testing may be safely omitted.

This report summarizes the results of immunization against diphtheria in more than 500 young adult student nurses during an eighteen-year period, with the use of several types of antigens and with a variance in the number and spacing of the injections. A number of subjects immunized from six to sixteen years previously were retested to determine the duration of the immunity.

Methods.—All student nurses of the Washington University Nurses' Training School were given Schick tests in groups of 15 to 50 early in their probation period during the years 1918-1935. Those with positive tests were immunized and were retested from four to six months later. This interval of several months before a retest seems important since in several instances Schick tests which were negative four to six weeks after immunization had again become positive three to four months later. Any who remained Schick-positive were given a second immunization identical with the first, usually from six to ten months after the initial injections. Previous to 1925 the Schick test toxin and immunizing antigens were obtained from the New York City Board of Health, and since then all material has been furnished by Eli Lilly and Company. Controls of the identical toxin preparation used for the Schick test heated for five minutes to 75° C. were always included, and readings of the tests and controls were made on the fourth day. All tests, readings, and im-

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munizations were done by the author to guarantee uniformity in interpretation and procedure. Some pupils who left training before immunization was finished are omitted from the tabulations, only those being included upon whom complete observations were made.

Results.—Susceptibility: Of 1,054 nurses tested, 664, or 63 per cent, gave positive Schick tests. A large proportion of these girls came from rural or suburban communities and a rather high percentage of susceptibility seems to be the rule in persons not reared in larger cities where diphtheria is endemic.

TABLE I

RESULTS OF DIPTHERIA IMMUNIZATION BY VARIOUS PROCEDURES

ANTIGEN USED	DOSES	INTERVAL	NUMBER VACCINATED	PER CENT NEGATIVE
1. T.A.T. (3L+)	3	1 wk. + 1 wk.	62	79.0
T.A.T. (2nd set)	3	1 wk. + 1 wk.	8	38.0
2. T.A.T. (0.1L+)	3	1 wk. + 1 wk.	274	59.3
T.A.T. (2nd set)	3	1 wk. + 1 wk.	96	92.6
T.A.T. (3rd set)	3	1 wk. + 1 wk.	5	100.0
3. Toxoid	2	3 wk.	53	75.5
Toxoid (2nd set)	2	3 wk.	13	92.4
Toxoid (3rd set)	2	3 wk.	1	100.0
4. Toxoid	2	5 wk.	46	78.2
Toxoid (2nd set)	2	5 wk.	10	100.0
5. Toxoid	3	3 wk. + 2 wk.	37	100.0
6. A.P. Toxoid	1	-	64	80.0
A.P. Toxoid (2nd set)	1	4-5 mo.	13	100.0

Immunization: The results of the immunizations with the various antigens have been summarized in Table I. In the two groups (1 and 2) with toxin-antitoxin (T.A.T.), it will be noted that a single series of three injections at weekly intervals did not regularly produce as high a percentage of immunes as might be expected. This was especially true of the 0.1L+ antigen which produced about 59 per cent of immunes. A second series of three injections resulted in the immunization of a very large proportion of the remainder, and the small number not immunized by the preceding injections became Schick-negative after a third set. The results with two doses of toxoid (Groups 3 and 4, Table I) given at an interval of three weeks or five weeks were quite similar to those from toxin-antitoxin. When three doses of toxoid (Group 5, Table I) were given at intervals of two and three weeks, the results were much better. A single dose of alum-precipitated toxoid resulted in only 80 per cent immunes, but a second dose immunized all the remainder. Although a few required a third set of injections with toxin-antitoxin and with toxoid, all became Schick-negative eventually.

In the immunization of infants and young children, it has been our experience, as well as that of others, that a rather high proportion of those inoculated with two doses of toxoid or a single dose of alum-precipitated toxoid develop negative Schick tests. There is a very definite impression, however, among certain health officers in rural communities that the response to diphtheria immunization is less satisfactory in rural children than that reported in cities. It may be that the relatively lower percentage of immunes obtained among the young adults here reported after their first series of injections is related to the fact that a large proportion of them were reared in suburban communities or that adults are more difficult to immunize with the same doses used in children. At any rate, the fact that, as a group, these nurses responded only moderately well to the initial vaccination gave a somewhat better opportunity to observe the relative effectiveness of the various procedures used.

Certain features of the results may be summarized briefly. Toxoid and especially alum-precipitated toxoid were relatively more effective than toxin-antitoxin. Two doses of toxoid or a single injection of alum toxoid immunized only 75 to 80 per cent. By far the best results were obtained by two doses of alum-precipitated toxoid, the second after a considerable interval, and by three doses of plain toxoid separated by intervals of several weeks. This tends to confirm the well-known experimental observations that the immunity following the first or "primary" response to the diphtheria antigen is slow, feeble and transient, but the "secondary" response following a later antigen stimulus results in rapid, pronounced and persistent antitoxin formation. It would appear, therefore, that those who become immune following a single injection or series of injections have already responded previously to the diphtheria antigenic stimulus such as occurs in the development of "natural immunity," and develop the permanent immunity characteristic of a "secondary" stimulus. On the other hand, those who have not reacted previously to the diphtheria antigen and consequently do not become immune following a single injection or series of injections will require a second immunization. It was hoped that alum toxoid, being insoluble and, therefore, slowly absorbed, would serve as both the primary and secondary stimuli and that a single antigenic injection would be adequate. The results in the series reported here, however, do not confirm this, since 20 per cent of those receiving a single dose remained Schick-positive.

The results obtained by the several methods used indicate that the maximum percentage will be immunized by two doses of alum toxoid with an interval of one to several months between them. While a considerable number may be immunized by a single injection, the percentage remaining Schick-positive is sufficient to warrant the advisability of giving a second later dose whenever possible. The larger number of

injections of toxin-antitoxin and plain toxoid make them less desirable for routine use, although the latter seems quite effective when given in three doses at intervals of about three weeks.

Reactions following toxoid injections are rare in infants and young children although often a somewhat tender nodule persists for some days after alum-precipitated toxoid. The occasional occurrence of moderately severe local pain and swelling accompanied by a febrile general reaction in older children and more frequently in adults has tended to limit the use of toxoid and alum toxoid. During the past six years several hundred young adults (nurses and medical students) have been given toxoid and alum toxoid. Most of them have had a slight local reaction only, while a few have had headache, mild fever, and malaise for the day following. Alum-precipitated toxoid seemed somewhat more likely to produce such an effect than plain toxoid. Rarely a very severe local reaction with general febrile toxic symptoms has occurred and persisted for several days.

In general, such reactions have been only slightly more severe than those following toxin-antitoxin and there has been no suggestion of discontinuing the use of toxoid because of them. It must be emphasized, however, that the foregoing applies only to the products of one manufacturer used routinely. In the few instances in which two other commercial toxoid antigens were tried, the number and the severity of the reactions were so great that they were considered unsuitable for use in adults.

Clinical Results.—All student nurses of the group tested spent from four to six weeks on duty in the contagious wards of the St. Louis Children's Hospital where they attended patients with clinical diphtheria as part of their training. During the three years immediately preceding the adoption of immunization in 1918, seventy student nurses were on duty in the contagious wards and twenty of them developed clinical diphtheria. Since 1918 only two cases of diphtheria have occurred among almost 1,000 students, both in known nonimmunes, accidentally exposed to the disease before immunization. This contrast in incidence before and after immunization is striking proof of the clinical effectiveness of the procedure in persons intimately exposed.

Duration of Immunity After Active Artificial Immunization.—The immunity which develops after diphtheria vaccination has generally been assumed to be lasting, although it is the general belief that in many instances the artificial immunity produced by injections merely protects the child over a certain limited period of susceptibility to diphtheria, and that during this time many develop an additional "natural immunity" which is solid and permanent. This belief is fostered by the frequent observation that even without artificial immunization there is a considerable tendency for older children and adults to have negative

Schick tests. That this tendency is apparently not constant, however, is shown by the fact that, in the adult nurses reported in this paper, 63 per cent were still susceptible. While in occasional instances diphtheria has occurred in vaccinated children, it has been extremely rare in those known to have been Schick-negative after vaccination. The published observations, however, on the duration of immunity based on Schick tests done some years after vaccination have been few because of the difficulty of collecting groups of immunized persons some years afterward. Such as I have been able to find are given in Table II. The first two show the results after toxin-antitoxin while the others report results with Ramon's anatoxin. The largest series, that of the Mosers (often mistakenly attributed to Ramon in the literature), gives somewhat misleading percentages, since no previous Schick tests had been made and many children may have been immune even before the anatoxin injections. In general, the results reported, however, indicate that the immunity

TABLE II

DURATION OF IMMUNITY AFTER ACTIVE IMMUNIZATION

OBSERVER		INTERVAL AFTER IMMUNIZATION—YEARS	NUMBER TESTED	PER CENT SCHICK-POSITIVE
Schroeder	T.A.T.	5	28	10.7
Parish and Okell	T.A.T.	1 to 4	440	5.0
Moser, M., and Moser, G.	Ana.	2	498	5.0
		3	162	4.3
		4	250	3.6
Cerruti	Ana.	2½	29	17.2
Calisti	Ana.	1	54 (adults?)	0.0
Bosco	Ana.	4	10	40.0
Ronchi	Ana.	5	27	14.8

persists in a large proportion of those vaccinated. Many of those found to have positive Schick tests later were observed to become reimmunized quickly after another vaccination.

In the groups of young adult nurses considered in this report, 102 were retested six to sixteen years after immunization by toxin-antitoxin and subsequent negative Schick tests. Of these, 12 had been done fourteen to sixteen years previously, and three of these, all after sixteen years, again gave positive Schick tests, one of them only weakly positive. Ninety who had received the injections six to twelve years previously included only two with positive tests, one of these (after nine years) being strongly positive and the other (after eight years) being only faintly positive. The fact that more than 95 per cent of this group of 102 were immune from six to sixteen years after vaccination is striking proof of the degree of effectiveness and persistence of the protection afforded by active artificial diphtheria immunization.

SUMMARY

In more than 1,000 young adult student nurses, 63 per cent were found susceptible to diphtheria by the Schick test.

Groups were immunized by toxin-antitoxin, toxoid, and alum-precipitated toxoid over a period of eighteen years. Of the methods tried, the most effective procedures were found to be (1) two injections of alum toxoid with an interval of several months between or (2) three injections of plain toxoid with intervals of several weeks between the doses.

As a result of immunization, the clinical incidence of diphtheria among these nurses has been reduced from 28.6 per cent to 0.2 per cent.

In a group of 102 nurses, immunized by toxin-antitoxin and retested six to sixteen years later, more than 95 per cent were still immune.

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MECHANICAL LESIONS OF THE APPENDIX IN CHILDREN AS A BASIS FOR APPENDICITIS

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THIS is an investigation based on the study of 127 consecutive cases of mechanical lesions affecting the appendix in children exhibiting symptoms not generally attributed to a disturbance of this organ, but clearly distinguishable by clinical and laboratory investigation. These findings were confirmed in all cases by careful study of the gross anatomical changes at operation, as well as by microscopic examination. In these lesions was found a basis for an explanation of a large number of cases of appendicitis in both childhood and adult life generally considered as acute primary forms. A diagnosis of mechanical lesions of the appendix was possible at such an early stage that by surgical removal of the causative factor the mortality rate was kept at a minimum. In this series it was zero.

It is also proposed to show that by early surgical intervention, not only is mortality reduced, but the nutritional development of the children, by its return to the normal, produces ideal weight and development.

This work on mechanical conditions in and around the appendix was suggested by the failure of some cases of bad posture in children to improve when abdominal supports were applied, or if they did improve they failed to maintain their improvement. In a certain number there were associated mild attacks of abdominal pain; a diagnosis of chronic appendicitis was made; and appendectomy was performed. At operation distinct mechanical lesions in and around the appendix were found and removed together with the appendix. The symptomatic relief and the nutritional improvement were so marked and rapid that they led to a very careful survey of similar cases; these after appendectomy had equally good results. This work clearly demonstrates the value of accurate laboratory work, the importance of very careful and detailed histories, and a diagnosis largely by exclusion.

Mechanical conditions involving the appendix have been described by numerous authors under the headings of "chronic appendicitis," and "appendical syndrome." The subject, "chronic appendicitis," has been a controversial one in surgical circles for years. Myers[1] quotes Watkins as reviewing 662 papers up to 1932 and reviews the literature to September, 1934. In his summary he states: "The more

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recent literature, especially that of the last five years, on chronic appendicitis indicates a growing opinion that there is such a malady, that it is more prevalent, more dangerous, and more frequently overlooked than has been previously taught. Indications are that failures of the past have been largely due to a lack of diagnostic thoroughness. Certain medical centers have published statistics showing from 60 to 90 per cent of the patients who had operations for chronic appendicitis were completely relieved by appendectomy alone. Muller recently (1932) has said that a campaign of instruction of the public regarding appendicitis is more important than a campaign against cancer. It seems fair to say that such a campaign should be directed to the laity regarding acute appendicitis, but a like campaign is needed for the profession regarding chronic appendicitis."

Freed[2] states, "In the United States and Canada twenty-five thousand die yearly from acute appendicitis, that is one death every twenty-five minutes, or seventy deaths every day, Sundays and holidays included, and the mortality is on the increase." In childhood there is an average mortality of about 14.5 per cent.

Farr[3] states, "I also believe that there is such an entity as chronic appendicitis and that it applies to children fully as often as to adults." Tenny[4] is convinced of the importance of a mechanical obstructive condition in and around the appendix as a producer of appendicitis, and he emphasizes reflex constipation and pylorospasm. Wilkie,[5, 6] one of the first to describe acute obstructive appendicitis, lays emphasis on constriction of the appendical lumen, with associated fecal concretions, and describes both an acute and a chronic form.

In making a diagnosis of mechanical conditions in and around the appendix, it is first necessary to know the normal anatomy. The appendix hangs down freely from the cecum and has a uniform and patulous lumen, and a terminal and limited arterial blood supply. Any kinking, twisting or constriction of the wall of the appendix, whether produced by Lane's bands, Jackson's membrane, short mesentery, or constriction of the lumen due to contracting fibrous tissue from a previous inflammatory reaction, will cause fecal retention, and this in turn will produce chronic irritation of the appendix. Through the sympathetic and vagus nerves, there is an intercommunication with the stomach, often producing pylorospasm with nausea or vomiting, or with the colon, producing spastic constipation.

When the lumen of the appendix is constricted, fecal material may be forced in from the cecum. But since the weaker contraction of the appendical wall is not able to evacuate completely the contents, a portion remains, and its moisture is absorbed through the appendical wall and produces a beginning inspissation which may lead to concretion. If this change is not severe enough to obstruct the lumen completely,

there are chronic symptoms, such as pain, spastic constipation, "bilious attacks," vomiting, etc. If the concretion completely obstructs the lumen, more severe changes may follow, often ending in gangrene. These cases produce, according to Wilkie,[5, 6] 90 per cent of the mortality of acute appendicitis. On the other hand, a constriction of the blood supply from a twist, short mesentery, membrane, or bands, causes edema of the wall and predisposes to an inflammatory process.

A typical history is that of a child who has had short attacks of recurrent abdominal pain for a considerable period, either daily or at longer intervals. The pain varies from a dull ache, a burning sensation, or sense of fullness to one of a sharp stabbing character. The attacks may be very fleeting but they have a marked tendency to recur, and at times there is associated nausea or actual vomiting. The *recurrence* of attacks, in spite of a well-regulated simple diet and good hygiene, is of great significance. Children often stop in their play, turn a little white, have a slight generalized abdominal pain, over in an instant. These cases are commonly diagnosed as indigestion. The pain is very likely to come on during or from one-half to two hours after a meal, or pains may have no relation to food intake. Pain frequently is increased by exercise, its location is umbilical or epigastrical at first, but later may become localized in the right iliac fossa. A bowel movement, passage of gas, or vomiting usually gives prompt relief. There are associated poor color, poor muscle tone, poor nutrition, and poor posture. Abdominal supports will often relieve the symptoms for a time, but there is frequently a recurrence. This failure to produce a permanent cure with abdominal supports is very suggestive. There is poor appetite, and constipation is the rule. The temperature, pulse, respiration, and blood count at this time are normal. A careful abdominal examination at the time of the attack will reveal in most cases slight deep right iliac tenderness with but little if any muscular rigidity. If a review of the family history reveals appendicitis in the near relatives, it is very suggestive, as heredity seems to play an important part; in this series the rate was 63 per cent. The physician should inquire as to any pylorospasm in infancy and any causeless attack of vomiting or cyclic vomiting, as in our 127 cases 66 per cent had vomiting and 6 per cent cyclic vomiting.

Later pain may move over to the lower right quadrant. A white blood count with careful study of the neutrophiles, including a nuclear shift, then shows slight irritative changes but not much elevation of the total count. As the case becomes more acute, there may be a slight temperature elevation during the attacks. At operation bands, adhesions, Jackson's membrane, a short mesentery, or stricture of the appendix with fecal concretions is found. The appendical lumen usually shows cystic dilatation and some atrophy of the mucous mem-

brane with a possible old fibrosis of the walls from a previously healed acute attack. If operation is performed very early in the course of the infection, no appendical lesion may be found.

Another frequent type is that found in a child who has been in apparently good health, but usually whose nutrition is poor, as shown by a searching history. He goes to bed to awake several hours later with sharp abdominal pain which causes him to double up. The pain is soon relieved, and he sleeps again only to awaken a second time with a return of colic, and he frequently vomits. At first the pain is in the umbilical region, acute and spasmodic; later it becomes less acute but more continuous, and becomes localized in the right lower quadrant. The temperature, the pulse, and the respiration are normal, but there is always a slightly anxious expression. These attacks of appendical colic may have numerous remissions. Examination during attacks shows deep right iliac tenderness. A prompt operation is indicated; at operation the appendix presents some form of constriction and contains inspissated fecal material or a concretion and often gangrene.

There is also a type of mild acute appendicitis, probably embolic, secondary to an infection from sinusitis, tonsillitis, etc. The patient has malaise and nausea, a furred tongue, loss of appetite, and constipation with a very slight temperature. There is vague abdominal pain at the umbilicus which later becomes more or less localized in the right side. The patient may be in bed a day or two, at the end of which time the symptoms gradually clear up. Deep iliac tenderness can be obtained, and if an operation is performed, edema of the appendical wall is found. It is often these overlooked attacks which cause inflammatory reaction with subsequent fibrotic stricture of the appendix.

There are numerous other combinations of symptoms neither so definite nor so suggestive of chronic appendicitis, but equally important to the child. A child who on automobile trips has nausea or actively vomits, or who has had periodic attacks of vomiting, either repeated mild attacks often in the morning before breakfast or severe ones with associated acidosis, probably has chronic appendicitis. He may, however, never have had any abdominal pain. A white blood count with a nuclear shift may show slight irritative changes, as increase in rod nuclears, in addition to changes suggesting a more chronic inflammation, as lymphocytosis and monocytosis. An examination of the abdomen at the time of a vomiting attack frequently discovers deep iliac tenderness and less often right rectus rigidity. These patients are treated as a rule for an imbalance of the sympathetic nervous system causing reflex vomiting and spasticity of the colon, resulting in colicky pains and constipation. A roentgen ray

study of the gastrointestinal tract may occasionally disclose a partially filling appendix which does not empty in the normal time (only one case in this series), but, as a rule, roentgen rays are not conclusive except as evidence of spasticity of the colon. Roentgen ray examinations were not used in this series on account of the expense and the fact that the diagnosis could be made without their aid. It was also felt that the barium and bismuth retained would complicate convalescence following operation. It is necessary to proceed with extreme

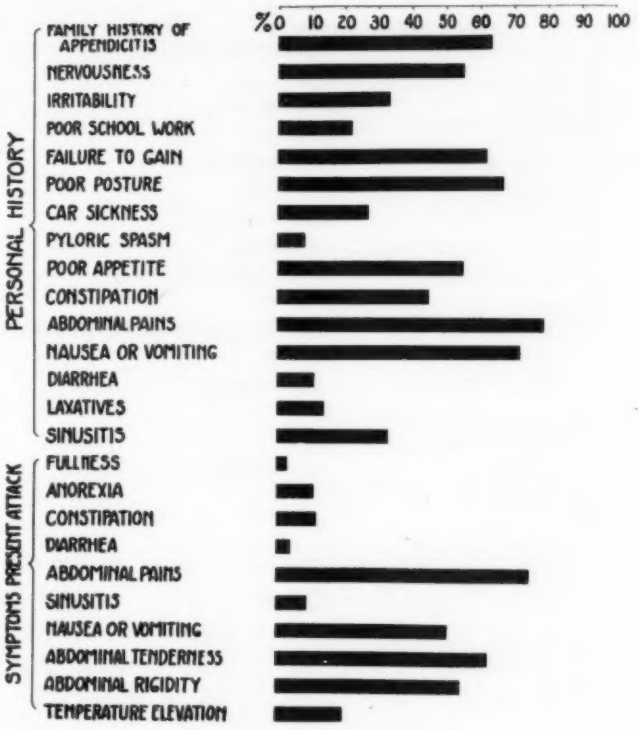


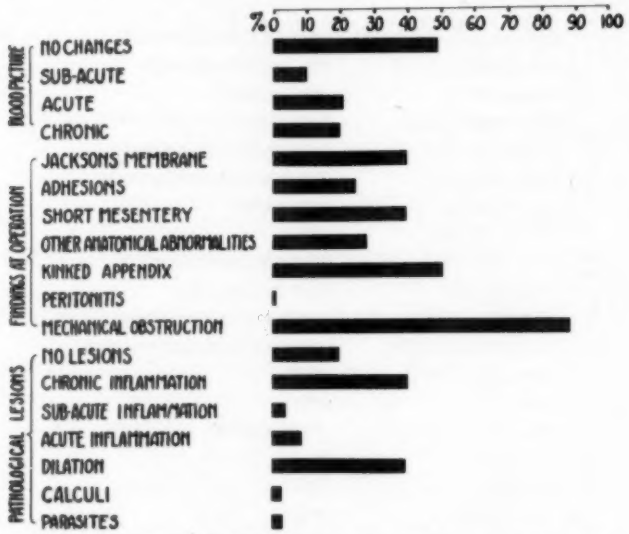
Chart 1.—Symptomatology.

caution and observe these patients for some time and to rule out any involvement of the genitourinary tract, by urinalysis and roentgenograms if necessary, but when by a process of elimination focal infections are excluded, one is justified in making a diagnosis of mechanical lesions in or around the appendix. Diagnoses are largely based on a history of long-continued symptoms and by elimination rather than by physical findings.

There is another group of children with definite symptoms of chronic appendicitis; in these the blood count usually shows an eosinophilia,

with an average of 4 per cent. Most of these patients in our series had seatworms in the appendix and were completely relieved by appendectomy. This condition was first recognized in 1899 by Still[7] and has been lately reviewed by Margaret Warwick.[8]

Once a diagnosis is established, an immediate appendectomy is undoubtedly the only treatment. In cases in which a diagnosis of chronic or mild acute appendicitis is associated with a sinusitis or other upper respiratory infection, one should operate at once. It used



APPENDIX:		NO LESIONS	CHRONIC	SUB-ACUTE	ACUTE	DILATION
BLOOD PICTURE	NO CHANGE	70	32			53
	CHRONIC	13	20	34		27
	SUB-ACUTE		14	33	11	13
	ACUTE	17	14	33	89	7

Chart 2.—Blood picture and pathologic findings.

to be our custom to delay operation until the infection cleared up, but we found that severity of the appendical condition is greatly increased, and there is grave danger of a gangrenous appendix and peritonitis if operation is delayed. By use of tribrom-ethanol (avertin) and the postoperative use of 10 per cent carbon dioxide and 90 per cent oxygen we have had uniformly good results.

In only one of our series of 127 cases was it necessary to use drainage. That patient was first seen two days after the onset of acute symptoms. Recovery was complete in thirty-nine days.

The most constant symptoms in our cases were attacks of abdominal pain, generalized at first, later sometimes localized with associated nausea or vomiting. The most common physical finding was deep tenderness in the right iliac fossa.

Charts 1, 2, and 3 give the frequency of occurrence of the various symptoms, findings at operation, pathologic conditions, and the results.

The pathologist in cases of chronic appendicitis must examine the appendix not only for signs of chronic fibrosis and acute inflammatory changes but also for evidence of cystic dilatation as is shown in microscopic section by flattening out of the rugae and also by atrophic changes in the mucosa.

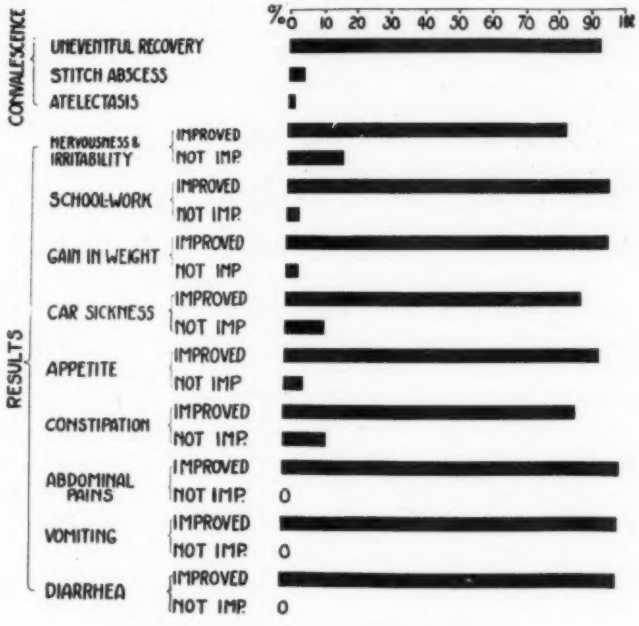


Chart 3.—Postoperative course and results.

In an analysis of the Bryn Mawr Hospital pathologic records of acute appendicitis in adults, approximately 95 per cent showed evidences of preceding fecal retention and cystic dilatation.

CONCLUSIONS

1. In 127 consecutive cases of mechanical lesions affecting the appendix in childhood, the symptoms usually began at an early age in mild form and recurred over a long period, the most constant being recurring abdominal pain, frequently associated with vomiting and deep right iliac tenderness.

2. In addition to complete recovery and relief from symptoms in all cases following appendectomy, the children showed a very notable increase in weight.

3. The extrinsic causes of obstruction of the appendix predominated, often leading to obliteration of the lumen and retention of fecal material.

4. Approximately 95 per cent of adult appendices removed at the Bryn Mawr Hospital showed evidence of obliteration of the lumen with fecal retention preceding the terminal inflammatory attack.

5. By a careful diagnosis in childhood and early operation, nutrition and development could be made normal at this age period, and mortality could be minimized at all ages.

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A STUDY OF THE BIRCH-HIRSCHFELD PHOTOMETRIC TEST FOR VITAMIN A DEFICIENCY

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VITAMIN A is one of the thirty-seven food substances essential for normal nutrition. A lack of this vitamin results in pathologic changes in many parts of the body. The most obvious changes are in the epithelial cells which tend to lose their columnar shape and become stratified. The occurrence of these changes in the conjunctiva and lacrymal glands results in the development of the eye condition known as xerophthalmia. This condition, however, develops only after an almost complete deprivation of vitamin A for many months.

Xerophthalmia is rarely encountered in the United States and Canada. During the past ten years at the Hospital for Sick Children in Toronto, we have seen only one case of xerophthalmia out of 802,000 attendances at the hospital. Similar figures indicating the rarity of this condition have been obtained from Harriet Lane Home, Johns Hopkins Hospital, Baltimore; the Children's Hospital, St. Louis; Minnesota General Hospital, Minneapolis; the Children's Memorial Hospital, Chicago; the Massachusetts General Hospital, Massachusetts Eye and Ear Infirmary, and the Children's Hospital, Boston; and the Montreal General Hospital, Montreal.[1] These findings are what one would expect when one considers the distribution of vitamin A in the foods ordinarily consumed. It is found in large amounts in the fats of dairy products, animal fats, liver, and egg yolk. Carotene, the precursor of vitamin A, is found in large amounts in spinach, chard, carrots, and many other vegetables and fruits. Vitamin A is probably the most widely and abundantly distributed of all the vitamins.

In harmony with this widespread and abundant distribution of vitamin A in foods is the absence of evidence of vitamin A deficiency at postmortem examination. At Boston, in the Children's Hospital, in 1,756 autopsies, keratinizing epithelial cells were demonstrated in only 15 patients.[2]

It is well recognized that night blindness may be caused by a lack of vitamin A. When this condition is present, the individual is unable to adjust his vision to decreasing amounts of light. The defect may be produced by a lesser deficiency of vitamin A than that necessary to cause

From the wards and laboratories of the Hospital for Sick Children and the Department of Paediatrics, University of Toronto, under the direction of Alan Brown, M.D., F.R.C.P.(C).

xerophthalmia. Demonstration of this defect, which can be present without any other obvious changes, might therefore indicate that the individual was suffering from a lack of vitamin A.

Reports have recently appeared in some European countries on the prevalence of night blindness.[3] Of much more interest and importance to us, however, are the reports of Jeans and Zentmire of Iowa City. These investigators found defective dark adaptation in 21 per cent of a group of children just admitted to the hospital.[4] In their more recent report of a survey of Iowa school children,[5] they found definitely subnormal dark adaptation in 26 per cent of the children from the rural districts, 53 per cent of the children from the villages, and no less than 56 to 79 per cent of the urban children, depending on their economic level. Furthermore, on the administration of vitamin A to 87 of these children with subnormal dark adaptation, they found either improvement or a return to the normal level in 84, or over 95 per cent.

These are most unexpected results. Although no details of the diets are given, it can be assumed that the diets are of the same standards as those used throughout most of the United States and Canada. Thus the work of Jeans and Zentmire would indicate that the average diet today does not contain an adequate amount of vitamin A.

The question of the adequacy of the supply of vitamin A is of such importance that we undertook an investigation using the instrument and technic as described by Jeans and Zentmire.[4]

The instrument used in making the test was a Birch-Hirschfeld No. 329 photometer obtained from Carl Zeiss, Inc. The photometer consisted of a metal tube 18 mm. in diameter with an electric light bulb in the end. At the other end of the cylinder there were in respective order, an opal glass, an iris diaphragm, and a second opal glass 40 mm. in diameter. The diaphragm was opened and closed by a lever with a scale marked with the diameter of the opening in millimeters. A metal disk, with five circles punched out, slid in a groove distal to the second opal glass. The holes were circular, 4 mm. in diameter. Four of the holes were situated in the form of a 2 cm. square. The fifth hole was in the center equidistant from all the others. In front of this was a Goldberg wedge, which is a glass slide with a uniformly increasing depth of opacity from one end to the other and marked off with a scale from 1 to 13, the numbers varying directly with the opaqueness.

The bulb in the metal cylinder was illuminated by a transformer connected to 110 volt circuit. The transformer stepped the voltage down to 3.5 in the light circuit. The source of light thus did not vary. The subject was placed in front of the photometer and observed the light from the bulb coming in the following order through opal glass, the iris diaphragm, opal glass, the fivepoint disk and the Goldberg wedge. The amount of light coming through varied directly with the size of the opening or scale reading of the diaphragm and inversely with the reading of the Goldberg wedge. Also because the wedge is graded from clearness to near opacity, the five points were not all equally visible. The end-point of the test was taken when the subject could definitely distinguish only three of the five points.

The examinations were carried out in a completely darkened room. The subject was placed with the head on a chin rest 24 inches from the photometer. The subject

faced a six-foot square-white screen placed at a distance of 40 inches from his eyes. Immediately behind the subject was a 150 watt electric light with a metal reflector which illuminated the white screen.

The subject, seated in the position described above, was directed to observe the middle of the screen for five minutes, estimated by the use of an interval timer. At the expiration of the time, the timer was again set for ten minutes. The lights were put out and the subject was directed to look at the photometer. He was asked to tell the number of points of light he could see. The Goldberg wedge was adjusted and the diaphragm opened or closed until the minimum amount of light was found at which the subject perceived constantly three of the five points of light. The instrument was covered for a few seconds with the hand to make sure that the subject was answering correctly. This is in accord with the technic described by Jeans and Zentmire.[4] They state, "The operator always confirmed the accuracy of an end-point by covering the wedge with the palm of the hand for a few seconds in order to rest the patient's eyes and then by having the subject again report on the number of points of light constantly visible."

Jeans and Zentmire[4] found that normal persons gave readings with the wedge set at 7 and the diaphragm at 14 to 20 at the first test, i.e., immediately after the eyes have been exposed to the bright light. It would appear that our light source before being reduced by a wedge and the diaphragm was of lesser intensity than that used by Jeans and Zentmire, as very few of the individuals we tested gave an initial reading with the wedge set higher than 5 and the diaphragm at 14 to 20 mm.

The subject will require more light for the first reading if it is taken immediately rather than a moment or two later. Thus it is impossible to make duplicate determinations of the end-point of the first reading because during the first few seconds after the room is made dark the recovery or adaptation is extremely rapid to a certain point and then slowly approaches the level that it reaches at the end of the ten-minute period in the dark. The latter level is the one which Jeans and Zentmire used to determine whether the adaptation was normal or not. They state that with their instrument the normal eye recovers to readings with the wedge set at 7 and the diaphragm at 3 to 6 mm., inclusive. In individual tests we confirmed that the second reading was constant by using different combinations of wedge and diaphragm settings which gave the same light values. At the end of the ten-minute interval the subject's ability to perceive does not vary as it does at the first test. Thus in considering the readings the one taken at the end of the ten-minute period is the important one. The smallest amount of light required by the subject after the period in the dark gives the greatest adaptation.

In the winter and spring of 1935, 163 subjects were tested for dark adaptation as outlined above. Eighteen of these were adults (laboratory staff and nurses), and 145 were ambulatory patients in hospital or attending the out-patient clinic. At this time we were interpreting our results in terms of the position of the Goldberg wedge and the size of the diaphragm opening. Because, as mentioned above, the instrumental readings obtained by us were in a different range from those of Jeans and Zentmire, we had to set our own normal level. We took the readings of 15 of the normal adults (laboratory workers and nurses) who were on a good dietary regime and used them as a standard. We decided that any reading with the wedge set at 7 or higher was normal. Using this standard, 53 of the subjects tested, or 32 per cent, showed poor dark adaptation. Twenty-eight of the group with poor adaptation to the

dark were given 2 teaspoonfuls of cod liver oil daily, and 18 of these, or 64 per cent, showed what we considered was improvement after a period of from two to six weeks' therapy. We believed that the above group were suffering from vitamin A deficiency and that we had confirmed the findings of Jeans and Zentmire.[4]

Later while carrying out further tests it seemed to us that there was an overlapping of the light values with different wedge settings and size of opening of the diaphragm. The physics department of the University of Toronto very kindly measured with a photoelectric cell the amount of light that was being transmitted to the subject at all the positions of the wedge and diaphragm. The measurements were made using the center light spot. The calibrations are given arbitrarily, allowing 1,000 for the wedge setting of 1 and the diaphragm wide open. Thus in terms of this apparatus, with a wedge setting of 1, diaphragm 20 mm. (wide open) the light value was 1,000 and with a wedge setting of 13 and the diaphragm of 2 mm. the value was 0.9. (Table I.) Any amount of light between can be obtained by suitable settings of the wedge and the diaphragm. The constancy of the light source was further checked by testing the transformer circuit with a sensitive voltmeter. The fact that the variations in potential were negligible indicated that the amount of light emitted by the lamp in the photometer did not vary.

We applied this table to the findings made in the winter and spring of 1935. It was observed that our arbitrary normal range obtained from the fifteen adults varied from 37 to 136. These adults were all taking what had been considered to be adequate diets, and, if we use this spread of readings for normality, then very few of our original group had poor adaptation.

In order to determine the optimum light adaptation we decided to test a group of children who were receiving more than adequate amounts

TABLE I

Light values for the photometer with the various positions of the wedge and diaphragm. This table was estimated for us by the Department of Physics of the University of Toronto. They measured with a photoelectric cell the amount of light transmitted to the subject through the center hole of the 5 points of light.

D* \ W†	1	2	3	4	5	6	7	8	9	10	11	12	13
20	1000.0	722.0	513.0	364.0	258.0	187.0	136.0	100.0	77.0	57.0	45.0	33.0	24.0
18	994.0	717.0	510.0	362.0	256.0	186.0	135.0	99.4	76.5	56.6	44.7	32.8	23.9
16	986.0	712.0	506.0	359.0	254.0	184.0	134.0	98.6	75.9	56.2	44.4	32.5	23.6
14	956.0	690.0	490.0	348.0	247.0	179.0	130.0	95.6	73.6	54.5	43.0	31.6	23.0
12	807.0	583.0	414.0	294.0	208.0	151.0	110.0	80.7	62.2	46.0	36.3	26.6	19.4
10	628.0	453.0	322.0	228.0	163.0	117.0	85.4	62.8	48.3	35.8	28.2	20.7	15.1
8	450.0	325.0	231.0	164.0	116.0	84.1	61.2	45.0	34.6	25.6	20.3	14.8	10.8
6	272.0	196.0	139.0	99.0	70.2	50.8	37.0	27.2	20.9	15.5	12.2	9.0	6.5
4	141.0	102.0	72.2	51.4	36.4	26.4	19.2	14.1	10.0	8.0	6.3	4.7	3.4
2	38.5	27.8	19.7	14.0	9.9	7.2	5.2	3.8	3.0	2.2	1.7	1.3	0.9

*D refers to setting of diaphragm.
†W refers to setting of wedge.

of vitamin A. To do this we tested 64 normal children from six to sixteen years of age, receiving in their daily diet 30 to 35 ounces of milk, butter, meat, fruit, two vegetables other than potato, cereal and bread. This diet supplies large amounts of vitamin A. In addition, they were given daily, 21,000 units of vitamin A* for a period of six weeks. It was found that this group required light values ranging from 19 to 258 for the test. The same children had been tested prior to the administration of the additional vitamin A and the spread of readings likewise was from 19 to 258. No difference was observed in the range of readings before or after the administration of the additional vitamin A. This is shown in Chart 1.

During the six-week period in which the additional vitamin A was being administered, the children were tested at biweekly intervals. In

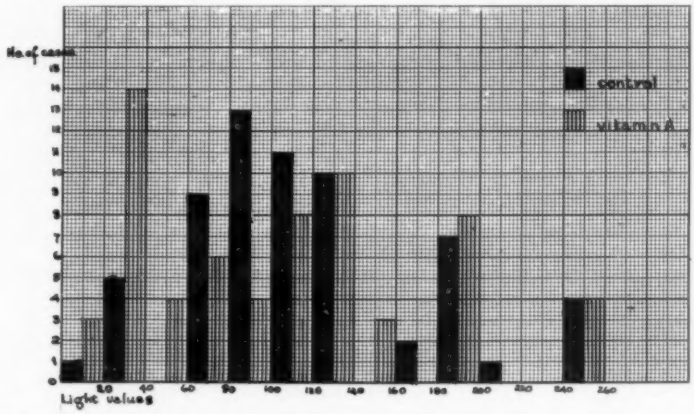

Chart 1.—Number of cases for the various readings for the test, before and after the administration of additional vitamin A.

Light value means the least amount of light necessary for the constant perception of the 3 points at the end of the ten-minute period in the dark. The cases are grouped with light values ranging from 0 to 20, 20 to 40, etc.

most cases the results obtained showed marked variations in the four tests on the same individual. A group of these selected at random are shown in Table II.

Because of the variability of the results we became concerned about the accuracy of the test. Dr. Walter W. Wright, chief of the ophthalmologic service of the Hospital for Sick Children, after examining the instrument and observing the technic of the test, stated that from his experience with other subjective eye tests with children he questioned the probability of obtaining reliable results.

In carrying out the test, the operator is entirely dependent on the veracity and personal reaction of the subject. If the subject reports

*Ten drops of viosterol in halibut liver oil. Kindly supplied by Mead Johnson and Company.

seeing three points of light, unless the light is turned out or covered so as to be hidden, the operator must accept that as what the subject sees. We found it absolutely impossible to test children under six years of age because of this, as their imaginations took them into realms away above the number of points of light on the instrument.

In order to rule out as far as possible factors which are difficult to control in children, such as imagination and personal reaction of the subject, twelve adults, physicians and technicians, working in the labora-

TABLE II

READINGS OBTAINED DURING THE ADMINISTRATION OF ADDITIONAL VITAMIN A*

SUBJECT	PERIOD OF ADDITIONAL VITAMIN A			
	0	2 WEEKS	4 WEEKS	6 WEEKS
I	19	85	45	37
II	134	85	130	45
III	208	117	45	130
IV	85	134	84	258
V	61	179	130	110
VI	37	37	130	110
VII	130	85	85	130
VIII	110	135	85	37
IX	247	151	110	184
X	85	136	179	26

*The lower the reading, the better the dark adaptation.

TABLE III

RECORDS OBTAINED FROM TESTS OF LABORATORY WORKERS AT APPROXIMATELY DAILY INTERVALS*

SUBJECT	TEST 1	2	3	4	5	6	7	8	9	10	11	12	13	14
A	116	163	116	208	116	179	163	179	50	85	84	85	84	50
B	70	70	116	36	186	151	84	151	179	179	179	151		
C	116	50	36	151	50	84	26	50	50	26	50			
D	26	84	37	85	26	50	50	26	37	50	26			
E	84	163	184	70	116	187	117	208	50					
F	37	50	26	50	26	50	26							
G	254	208	228	208	116	179	151							
H	208	208	163	116	163									
I	84	247	50	50	247									
J	184	70	184	84	117									
K	186	151	117	151										
L	116	151												

*The lower the reading, the better the dark adaptation.

tory were tested daily for varying periods. There was no change made in the routine of these individuals. The record of the tests from these subjects is given in Table III. Two consistently required a small amount of light to perceive the points; 3 consistently required a large quantity; 4 varied from day to day; 2 improved and 1 became less adapted to the dark as time went on. Also the subjects would observe when the light was near the limit of perception, that they saw 3, 2, 0, 5, etc., points when the source was not varied in any respect. The statement was also

made that the lights were being moved. Our tests with adults showed wide variation for individual subjects, similar to the results obtained with the children.

It was pointed out to us that adaptation to the dark may be somewhat a matter of experience. Persons living in rural districts have little difficulty going about in the dark because they have good adaptation. However, the same individuals residing in urban centers for a period lose that ability and then will regain it when on a vacation in the country after a week or so.

CONCLUSIONS

In our hands the Birch-Hirschfeld photometer has been unsatisfactory for the estimation of small variations in dark adaptation, such as might be produced by vitamin A deficiency.

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CARBON TETRACHLORIDE POISONING

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INSTANCES of carbon tetrachloride poisoning have been frequently described.[1-4] Without attempting a comprehensive review, we are reporting an additional case, partly because the drug was contained in a common household material, but principally because clinical discussions of the treatment of this intoxication have been rare.

USES FOR CARBON TETRACHLORIDE

Most instances of poisoning from this drug occur because of its use in certain fire extinguishers, in various cleansing solutions, and in the treatment of hookworm disease. The fact that its vapor is heavier than air makes it valuable to the fire fighter, but dangerous to the recipient of a "dry" shampoo who breathes the intoxicating fumes that settle around her face,[5] or to one using the chemical as a grease remover inside a closed automobile. Poisoning due to absorption through the gastrointestinal tract has occurred chiefly in the treatment of hookworm disease.

PROPHYLAXIS

The Egyptian Board of Health in its wholesale treatment of villages for hookworm disease has found carbon tetrachloride intoxication occurring often enough with the therapeutic dose of 4 c.c. to warrant a routine set of precautions enforced within the temporary compounds where all treatments are given. The routine may be briefly outlined as follows: All persons who have recently taken alcohol are refused treatment. Ascaris infection also is considered a contraindication to the use of carbon tetrachloride because of the possibility of obstruction to its rapid excretion. All persons to be treated are placed on a high carbohydrate, low fat diet by advance agents. Immediately before the therapeutic dose of carbon tetrachloride, sugar in the form of molasses is given each patient. Following the administration of the carbon tetrachloride, each patient receives a saline cathartic. Patients may not leave the compound until the purge has proved effective. Those showing toxic symptoms are treated immediately with calcium and glucose.

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PHARMACOLOGY

The drug is absorbed through the gastrointestinal tract, the lungs, or injured skin.[7] Overdosage may cause hemorrhages in the gastrointestinal mucosa, albuminous infiltration of the glomeruli of the kidneys, and central necrosis with cirrhosis or terminal acute yellow atrophy of the liver.[3, 4] Lipemia has been a frequent finding.[3, 4] Toxic symptoms progress through vomiting, stupor, temporary recovery, jaundice, fever, amblyopia, edema, anuria, hematuria, albuminuria, convulsions and coma, to death. Alcohol, fat, or protein in the diet increases the drug's toxicity.[7, 9] High carbohydrate and calcium intake reduces intoxication and frequently is associated with recovery.[7, 10]

Minot and Cutler[11] have pointed out a guanidinemia in carbon tetrachloride poisoning which they believe is responsible for interruption of carbohydrate metabolism. They believe that glucose is not resynthesized from lactic acid and that this results in both a hypoglycemia and an accumulation of lactic acid in the blood and its excretion in the urine. Finding that guanidine and calcium are antagonistic[11] and believing that calcium is necessary for activating the adrenal mechanism that normally compensates for a low blood sugar,[10, 12] Minot and Cutler feel that intravenous glucose becomes permanently effective in compensating for the hypoglycemia only when given with calcium.

CASE REPORT

The two-year-old boy (weight 25 pounds) who stimulated our interest in this type of poisoning was brought in on April 9, 1935, two hours after swallowing 1 to 25 c.c. of the noninflammable cleaning fluid Energine (90 per cent carbon tetrachloride, 10 per cent hydrocarbon with petroleum base).[13*] He had vomited immediately and become drowsy. Physical examination on admission showed no abnormalities except stupor and the odor of carbon tetrachloride about his mouth. The essential feature of his treatment, which started immediately, was the intensive administration of glucose and calcium with a minimal fat and protein intake. Milk and fruit juices were the only foods allowed. Parenteral fluids were given on each of the first six days of the intoxication. The details of treatment are given in Table I.

Within twelve hours he was up playing around the crib, seemingly normal. The second day he refused to eat, had a temperature of 104° F., and a urine containing a trace of albumin, 2 red blood cells, 2 white blood cells, and occasional granular casts in each high dry field of an uncentrifuged, voided specimen. The blood at this time contained 80 per cent hemoglobin (Tallqvist), with 4,500,000 normal red cells and 25,000 white cells per cubic millimeter; 95 per cent of the latter were polymorphonuclear. On each of the first three days he vomited twice and had 5 stools which, though watery yellow, contained no blood, and grew no typhoid or dysentery organisms when cultured.

On the third day he refused to eat and was irritable. The temperature rose again to 103° F. (pulse 160), and at 6:00 P.M., following a few generalized twitchings, he

*This particular product carried no announcement on the label to indicate either its chemical or toxic nature.

TABLE I

CHEMISTRY OF THE BLOOD							CLINICAL STATE	THERAPY (IN C.C.)										
								INTRAVENOUS					S.C.	INTRAMUSC.		ORAL		
DAY OF DISEASE	CO_2 VOL. %	N.P.N. MG. %	SERUM PROT. GM. %	CALCIUM MG. %	CHLORIDE M. EQ./L.	ICTERIC INDEX		10% GLUCOSE	20% GLUCOSE	50% GLUCOSE	10% CB GLUC.	PLASMA	NORMAL SALINE	10% CB GLUC.	LIVER EXTRACT	SKIM MILK	FRUIT JUICE	CALCIUM LACTATE
1	57	27	6.8	10.2			Stupor in A.M. Lively in P.M.	200 200			15 10					800	800	
2							Anorexia	200			10		300				1,100	5 gr. 5 gr. 5 gr.
3				7.0			Listless in A.M. Convulsions and unconscious in P.M.	200	 120	 25	10 20		300				500	5 gr. 5 gr.
4	30	45	3.5	10.0	90		Semicomatose Liver 1.5 cm. Slight jaundice		130 130 130		10 10 10	 140	350				250	
5	38	60	4.5		90	15	Semicomatose Liver 3 cm. Slight edema		100 100		10 10			10 10	5	1,200 gav.		
6		64	4.5	11.0	90	15	Interested in surroundings Edema, ascites, anuria		200	25	10			10		700 gav.		
7	50	68	4.5		90	15	Brighter Anuria, edema								5	780	600	15 gr.
8							Playing; voiding Liver at umbilicus									780	600	15 gr.
9	50	88	4.5			10	Playing Edema and ascites less Liver 3 cm.								5	Soft solid diet with whole milk from this point on.		15 gr.
10							Sitting up											15 gr.
11																		15 gr.
12		80	5.8				Liver 2 cm.											15 gr.
13																		15 gr.
14		40		11.8			Liver 1.5 cm.											15 gr.

suddenly became rigid, cyanotic, pulseless, and unconscious, breathing irregularly. Intravenous sodium luminal (1 gr.) was ineffective. Ether relaxed the rigidity and clonic twitchings slightly; after receiving 25 c.c. of 50 per cent glucose intravenously at 7:30 P.M., the extreme rigidity of his early attack relaxed; moderate opisthotonus and mild twitchings still remained at 11:30, when he received 120 c.c. of 20 per cent glucose with 20 c.c. of 10 per cent calcium gluconate intravenously. At this time the blood pressure was 100/78; there was no papilledema. Spinal fluid collected at this time was normal. After midnight he was completely relaxed.

During the fourth and fifth days he was semicomatose and was fed chiefly by gavage. The liver for the first time became palpable, increasing in size so rapidly that by the seventh day it was at the level of the umbilicus. There was never real jaundice. Peripheral edema, ascites, and anuria were the prominent clinical findings from the fifth to the eighth day. The urine continued to show cells, casts, and appreciable albumin until the ninth day; it was normal thereafter. By the end of the second week edema and ascites were gone; the boy was sitting up playing in bed and eating a soft solid diet enthusiastically. The liver receded slowly and at the time of discharge, three weeks after admission, was still 1 cm. below the costal margin.

Three months after discharge he was reexamined. His appetite was poor. He had not gained weight. The liver edge was not palpable. When given 25 gm. of galactose by mouth, he showed no reducing substance in the urine collected for the next six hours. Phthalein excretion was within normal limits and the nonprotein nitrogen at this time was 23 mg. per cent.

COMMENT

It would be presumptuous to attach much significance to the limited data represented by this case. Yet certain points are of interest.

In the presence of the low chlorides, a constant hematocrit (4,500,000 red cells per cubic millimeter on the fourth day), and a rising nonprotein nitrogen level, it could be assumed, according to the theories of Minot and Cutler, that the low CO_2 was related to the accumulation of lactic acid in the blood. Whether the severe convulsive episode on the third day was due to hypoglycemia must remain uncertain, inasmuch as studies of the blood sugar were not made during the acute phase; the blood calcium just an hour before the attack was low enough to make it conceivable that tetany may have played a part. We could not help but be impressed by the possible significance of calcium and glucose in the treatment of this intoxication. In the presence of adequate hydration we felt that the urinary findings, anuria, and the nonprotein nitrogen represented definite renal injury. We wondered whether the abrupt fall in serum protein was due to liver damage or to starvation. Liver extract was given because of certain evidence that it has a substitution value in instances of acute hepatic damage.[14] Plasma was used in transfusion because of the low serum protein and adequate hematocrit.

Because there have been so few clinical reports of recovery from a severe poisoning by this drug and because the therapy or theories in-

volved are not well known, we are including in our report the following outline for the study and treatment of similar cases:

a. Emergency gastric lavage; catharsis.

b. Low fat, low protein, high carbohydrate diet.

c. Calcium intake maintained at 0.5 gram intravenously, or 2.0 grams by mouth, daily.*

d. If vomiting is predominant, continuous intravenous drip (calcium gluconate, 5 per cent glucose, normal saline).

e. Parenteral fluids and transfusion as indicated.

f. Studies of blood sugar, CO_2, nonprotein nitrogen, calcium, serum protein, fat, guanidine, and lactic acid.

SUMMARY

We have reported an instance of severe poisoning from carbon tetrachloride contained in a common household cleaning fluid and have emphasized certain forms of available therapy, notably the intensive use of calcium and glucose.

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*One gram of calcium is contained in 1,000 c.c. milk, 10 gm. of calcium gluconate, 4 gm. of calcium lactate, or 3 gm. of calcium chloride.

Correspondence

The Relation of Tuberculosis to Generalized Atypical "Tuberculosis" Adenitis—A Manifestation of Lymphogranulomatosis Benigna (Schaumann)

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In a recent number of THE JOURNAL OF PEDIATRICS, A. Wilmot Jacobsen in a paper, "Generalized Tuberculosis of the Lymph Nodes and Multiple Cystic Tuberculosis of the Bones," has reported what he claims to be a case of proved tuberculous disease in a child in good general condition, who failed repeatedly to react to large doses of tuberculin.

To his statement, "With the Mantoux test, except the false negative reactions during the acute stage of some of the febrile diseases and in moribund patients, and those with overwhelming infections . . ., we have never seen another case of proved tuberculosis in a child who persistently gave a negative tuberculin test," can be added that the same rule holds true for the adult as shown by Hart[1] and Lichtenstein.[2] This rule is founded on a vast material of clinical and pathologic studies and is of the greatest value to the clinician and to the pediatrist. As Jacobsen claims to have described a case which is an exception to this rule, his statement is of the greatest interest from the standpoint of the biology of tuberculosis. If his case is studied in the light of recent investigations, however, doubt arises that his case is a proved exception to the above mentioned rule. The reasons for this are the following. The type of lymph gland enlargement in his two cases, as he states, are of the same characteristic type, both clinically and histologically, as seen in Boeck's sarcoid. The disease of skin and mucous membranes "sarcoid Boeck-Besnier," the osseous condition of "osteitis multiplex cystoides" of Jungling, the lymph gland swelling of the type mentioned above, together with certain forms of pulmonary disease and splenomegaly have been grouped together by Schaumann[3] under the term "lymphogranulomatosis benigna" as manifestations of a general systemic disease with many points in common with Hodgkin's disease. The recent communications of Mylius and Schürmann,[4] Pautrier,[5] Salvesen,[6] Kissmeyer,[7] Chevallier and Führer,[13] and Nielsen[14] may be referred to for the details of interpreting these conditions as manifestations of the same systemic disease. The etiology and pathogenesis of benign lymphogranulomatosis, as well as of Hodgkin's disease, are obscure. Some hold that it is a disease *sui generis* with its own etiology—an unknown infectious agent (Kissmeyer[7]); others hold that it is merely a syndrome—a mode of reaction to different agents as tuberculosis, leprosy, or lues (Darier[8]); while a large group of clinicians hold that the disease is a special form of tuberculosis with a very low allergic reaction ("positive anergie," Martenstein and Noll,[9] of the Breslau Dermatological School).

Whatever may be the etiology, it is far from being proved as tuberculous in nature. Jacobsen states (p. 305), "It is reported that the tuberculin test may be negative in lupus pernio, Boeck's sarcoid, and osteitis multiplex cystoides, as for example in Jüngling's Cases 2, 3, 7 and 9. These, however, and most of the other similar cases in the literature, were tested by the relatively insensitive Pirquet method, and it is by no means assured that the intradermal tests with the stronger dilutions would likewise have failed to produce positive tests in these individuals."

The following data show that a complete lack of reaction is seen in about one-third of the cases. Martenstein and Noll[9] found 5 of 16 cases of lupus pernio and Boeck sarcoid negative to 0.1 mg. of tuberculin intracutaneously. Danbolt[10] found 7 of 11 cases of Boeck's sarcoid negative with 5 to 50 mg. Bonnevie and With[11] found 7 of 23 cases negative to 1 mg., and of these 4 also were negative when tested with 10 mg. In light of the extensive work of Hart[1] this should be considered as a strong argument against the tuberculous nature of the disease.

If the cases of Jacobsen are reviewed in light of their findings, the following points may be considered.

1. The two children suffer from a typical benign lymphogranulomatosis. Case 1 of the glands, bones and lungs, Case 2 of the glands and lungs only.

2. Both children have been exposed to infection with the tubercle bacillus by the father who was at home with open pulmonary tuberculosis from July, 1930, to January, 1934.

3. With these facts in view, the following explanation is at hand;

The first child with the strongly positive tuberculin reaction has besides her benign lymphogranulomatosis a tuberculosis which has nothing to do with her primary disease. The fact that she died after a couple of years from generalized tuberculosis has no influence on this statement. Tuberculosis has been reported several times as a complication which has been the cause of death in both benign and malignant lymphogranulomatosis.

It is to be noted in Case 2, with the negative tuberculin reaction, that the reactions were not performed after January, 1933, and the child did not die until May 31, 1934. In the interval, January, 1933, to May, 1934, she was at home at the same time as the father and had opportunity to be infected with tuberculosis. Moreover, the fact that she was infected with tuberculosis and died from tuberculous meningitis within this interval is in agreement with the findings of Wallgren and Nilson[12] that meningitis follows as a rule a few months after primary infection. The question remains as to why she was infected so late, as she had been living with, and exposed to, the father previously. It may be answered that in an exposed family some children are infected early while others avoid infection for a long time (Hart[1]).

4. As this child, provided that the interpretation is correct, was not infected with tuberculosis at the time of the negative tuberculin reaction, the case is not contradictory to the doctrine of the absolute value of the negative tuberculin reaction.

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Remarks to the Foregoing Paper of Torben K. With, "The Relation of Tuberculosis to Generalized Tuberculous Adenitis—A Manifestation of Benign Lymphogranulomatosis"

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The histologic diagnosis of the lymph nodes in both of the cases published by one of us (A. W. J.) and the postmortem examination in Case 1 were made by the other (K. L. T.). Therefore, we feel that we ought to comment jointly on the foregoing paper of Dr. Torben K. With, which is based solely on citations from the literature of cases more or less similar to ours. We feel that more emphasis should be placed upon the pathohistologic features than was done by Doctor With. First, however, we wish to note a distinct disagreement as to the nomenclature. There is a most unfortunate tendency in present-day medicine to create new names for combinations of pathologic lesions which heretofore have been known under less misleading simple descriptive terms. One of these new names is "benign lymphogranulomatosis." It was introduced by Schaumann[1] to designate tuberculoid granulomas in lymph nodes, skin, bone marrow, lungs, and sometimes in tonsils, and probably also in the spleen and liver. The characteristic histologic feature in all these organs is typical epithelioid cell tubercle formation, usually with absence of caseation, although slight central necrosis may be present, especially in the lymph nodes. This name has not been adopted by pathologists. Mylius and Schürmann[2] speak of the same lesions in lymph nodes as "universal tuberculous large cellular hyperplasia." They call attention to the later stages with hyaline sclerosis instead of caseation and calcification. They consider these lesions as a peculiar form of atypical tuberculosis, identical with the systemic large cellular hyperplasia described long ago by Ziegler. This hyperplastic type of lymph node tuberculosis is well known to all pathologists. Some of them prefer the term "fungoid," designating tuberculous granulation tissue without caseation.

In discussing the etiology of "benign lymphogranulomatosis," Doctor With fails to mention that Schaumann,[1, 3] who originated this term, and also Schürmann and Mylius, interpret these lesions as atypical tuberculosis in an etiologic sense. The causative agent in their opinion is a tuberculous virus. Schaumann tried to explain the absence of the tuberculin reaction by a state of anergy or a sensibility to tuberculin. We wish to call attention to the discussion of Schürmann and Mylius of their own cases, one of which showed a combination of tuberculous lymph node hyperplasia and ordinary progressive tuberculosis of the lungs. They state that "the negative reaction to tuberculin in pure cases of tuberculous lymph node hyperplasia should not impress us as being so strange when we consider the entire histologic picture, especially the absence of caseation. However, behind this symptom (i.e., the negative reaction) there are more problems hidden, which at the present time cannot be answered." These authors discuss further the different possible combinations of the noncaseating tuberculous hyperplasia with the ordinary tuberculosis. These two varieties may appear simultaneously, or a more caseating type may complicate a mere hyperplastic tuberculosis at a certain time which at postmortem examination may be estimated from the anatomic findings. This latter type possibly could be produced by two different tuberculous viruses. In most cases, however, it is, according to Schürmann and Mylius, impossible to learn anything certain about the time at which caseating tuberculous processes may appear in a patient suffering from tuberculous lymph node hyperplasia. On the other hand, in their opinion, this combination of the caseating and noncaseating types especially suggests the tuberculous etiology of the epithelioid cell hyperplasia in lymph nodes (so-called "benign lymphogranulomatosis").

If as careful an observer as Schürmann admits the difficulty inherent in any attempt to analyze these cases of combined atypical and ordinary caseating tubercu-

losis in exact pathogenetic and etiologic terms, it is rather surprising to see the readiness of Doctor With to explain either the presence or the absence of the tuberculin reaction in our two cases. Doctor With bases his discussion on the assumption that the noncaseating or fungoid type of lymph node tuberculosis is not tuberculosis at all in an etiologic sense and that in both of our cases there were two different diseases which had nothing to do with each other. The literature which Doctor With himself quoted, especially the papers of Schaumann, and Schürmann and Mylius, suggests strongly that his interpretation is not necessarily correct. How can he feel sure that the benign lymphogranulomatosis was the "primary disease" and that only later as indicated by the positive tuberculin reaction a real tuberculous infection occurred? How did this "primary disease" enter the body? There was ample opportunity for tuberculous infection in the home of this negro family through all the years in which the two children were seen. The term "benign lymphogranulomatosis" was not used in our paper for reasons mentioned herein, just as Schürmann and Mylius, like many other pathologists, prefer the term "atypical lymph node tuberculosis." As to the etiology, in addition to Schaumann, and Schürmann and Mylius, Beintema[4] and Jadassohn[5] speak of tuberculoids. There are, of course, other dermatologists, especially of the French school, who do not feel that epithelioid cell granulomas in the skin and lymph nodes are tuberculous in nature, among these especially Pautrier.[6] However, to introduce still another designation for this syndrome, as Pautrier does in speaking of "reticulo-endotheliose," seems to us inappropriate inasmuch as the term is already markedly overburdened and used for entirely unrelated diseases.

We strongly recommend discarding the term "benign lymphogranulomatosis," as it has proved to be confusing, especially when used to suggest a relationship to tuberculosis similar to that borne by Hodgkin's disease. Indeed it inevitably implies such a similarity, as in many European countries the term "lymphogranulomatosis" is used synonymously with Hodgkin's disease, which condition in a high percentage of cases is entirely unassociated with tuberculosis. With regard to this question, we might refer to the paper by one of us[7] dealing with the nature, pathogenesis and etiology of Hodgkin's disease.

From the postmortem findings in our first case it is clear that the tuberculous infection occurred several years previous to death. Several calcified foci were found in the parenchyma of the lungs. When and why at a later time the picture of tuberculous peritonitis and caseating bronchogenic spread in the lungs was brought about is just as difficult to explain as in so many other cases of chronic tuberculosis in children and adults. The entire complex question of exogenous reinfection or endogenous exacerbation should be carefully examined in all cases of this type. Inasmuch as in our second case a complete postmortem examination was not performed, we would prefer not to comment on the relation of the progressive tuberculous lesion terminating in tuberculous meningitis to the tuberculous lymph node hyperplasia. There is, however, no reason to assume, as Doctor With does, that we are dealing with a recent tuberculous infection, which resulted in tuberculous meningitis. The first infection with tubercle bacilli may have occurred several years previous to death in this case just as well as in the first one. To the statement of Doctor With, based on a quotation of Wallgren and Nilson that tuberculous meningitis follows as a rule a few months after the primary infection, which he uses to prove the recent nature of the tuberculous infection in Case 2, there is a large number of exceptions in children and adults. We could cite from our own material several postmortem protocols proving that tuberculous meningitis is found in children and adults with entirely stony tuberculous complexes.

The fact that we do not understand the tuberculin reaction in the individually different types of tuberculous tissue processes, especially in the purely hyperplastic type, should make us very careful not to arbitrarily dismiss the possibility of tubercu-

losis on the evidence of a negative tuberculin test alone. All the environmental factors, the family history, signs of tuberculous infection in all children, linked with the anatomic histologic findings in both of our cases speak strongly for a common tuberculous etiology. The histologic picture is that of atypical epithelioid cell hyperplasia. There is so far no other etiologic agent known which can bring about a universal tuberculous lymph node hyperplasia with epithelioid cells and Langhans' giant cells, with or without slight central necrosis, except the tubercle bacillus or a tuberculous virus in a wider sense.

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Critical Review

TUBERCULOSIS IN CHILDREN

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THE most comprehensive survey ever undertaken of the facilities for caring for tuberculous patients in the United States has been completed by the Council on Medical Education and Hospitals of the American Medical Association and was fully reported in the December 7, 1935, issue of the *Journal of the American Medical Association;*[1] 471 sanatoriums, 740 tuberculosis departments of hospitals, and 29 preventoriums provided the statistical data upon which the report is based. The total capacity for tuberculosis is 95,198 beds: 64,997 in the sanatoriums, 28,534 in the tuberculosis departments, and 1,667 in the preventorium group. The total replacement value of the tuberculosis institutions is estimated at approximately $328,937,777.36, or a general average of $3,455.30 per bed. The annual cost of the tuberculosis hospitalization in the United States exceeds $70,000,000. The average cost of maintaining a tuberculous patient in the sanatoriums is $2.37 a day; in the tuberculosis department, $2.95; and in the preventoriums, $1.39.

More pertinent for the purposes of this review is that part of the report which deals with children. A total of 11,647 beds are available for this group of patients in all the tuberculosis institutions. Of these the sanatoriums provide 9,036; the tuberculosis departments of hospitals, 944; and the preventoriums, 1,667. All together, 230 sanatoriums admit children. Over half of the sanatoriums admitting childhood tuberculosis also admit children with pulmonary tuberculosis of the adult type. The figures given for admissions to the tuberculosis sanatoriums show that of a total of 12,629 children, 1,191 had adult type tuberculosis; 6,659, the childhood type; 824 had extrapulmonary lesions; 3,236 were nontuberculous; and 701 were unclassified. Sixteen of the twenty-nine preventoriums reported 2,479 patients admitted, of whom 12 had the adult type tuberculosis; 424, the childhood type; 24 had extrapulmonary lesions; 1,326 were nontuberculous; and 693 were unclassified. The report further states that many of the sanatoriums admitting children have a waiting list for adults and properly questions the wisdom of such a procedure, pointing out that the prime objective in tuberculosis control is the isolation of tuberculous patients who give off tubercle bacilli. For the most part, the report indicates that the children in tuberculosis institutions received adequate protection from "open" cases of tuberculosis, but that in some there were opportunities for contact between adult patients and children, and in a few sanatoriums it was observed that children with pulmonary tuberculosis were hospitalized together with other children in the preventorium unit.

It is rather surprising to learn that over 37,000 tuberculous patients were admitted to general hospitals in a one-year period (1934). Undoubtedly the majority of these institutions provide adequate segregation facilities, but it is a fair surmise that there are many thousand other unrecognized tuberculous patients admitted to hospitals in general who are a source of contagion for other patients, nurses, doctors, and attendants. That such a surmise is correct is attested by observations on nurses and medical students among whom the percentage of positive reactors to tuberculin is relatively low at the beginning of training, but approaches 100 per cent by the time the training period has been completed. The medical profession as a whole still pays too little attention to the communicability of tuberculosis. The time is not far distant when the same contagious technic will be applied to the care of tuberculosis as is now applied to diphtheria and scarlet fever. In fact it is not improbable that within a few years it will have become the custom in many of our hospitals to require satisfactory evidence of the absence of tuberculosis in a communicable form before the admission of the patient to the general wards. This could be accomplished at slight expense by means of routine fluoroscopy for all patients over ten years of age. Such a procedure should be but little more troublesome than the requirement of throat cultures and vaginal smears enforced in many pediatric departments and should reduce the hazard to doctors and nurses, as well as benefit the patient. If it were carried out in obstetrical departments, loss of life among infants due to fatal forms of tuberculosis could be materially reduced.

Another point worth dwelling on briefly and which the report brings up is the matter of institutional care of children who are in contact with tuberculosis in their homes or who have only the first infection type of tuberculosis. From the report it will be seen that there were many such admitted to sanatoriums and preventoriums. Obviously a considerable sum of money was involved in the care of these children. Was it worth it, or could this money have been spent to better purpose in other ways?

Myers[2, 3] believes that knowledge gained from years of observation of large numbers of children with primary tuberculosis has amply demonstrated that these children do not need treatment in sanatoriums, preventoriums, special schools, fresh air classrooms, or summer camps, to heal their tuberculous foci. Treatment in such institutions neither hastens the healing process nor makes it more complete than that which occurs in the child's own or a foster home. If the child remains in his own home, it is of course desirable that the infecting source be removed. He cites as substantiating evidence of his opinion the results of treatment in 155 children who were observed from the time the disease was in the acute inflammatory stage until lime or fibrous strands were deposited in sufficient quantity so that they could be visualized in the x-ray film. Nineteen were treated in sanatoriums; 50 in the Lymanhurst school; and 86 in their homes. Among 136 whom it was possible to trace, no difference could be seen in the course of the disease, whether the children were treated as strict bed patients, sent to a special school, or remained as active as any normal child is in the home. Consequently, Lymanhurst has discontinued its treatment division and has diverted its funds into other channels of tuberculosis control.

Nor "have we been able," states Myers,[2] "to obtain any evidence to show that hospitalization, special schools, summer camps, or any other form of treatment except breaking contact with tubercle bacilli has any influence upon the later development of reinfection type of disease." Again the point should be made that the admission of a child to a tuberculosis institution does not insure that contact with tubercle bacilli will be prevented. On the contrary, the opportunities may actually be increased.

In addition to the argument that institutional treatment of first infection tuberculosis is unnecessary, the proponents of this line of reasoning draw attention to its futility. For instance, Myers[2] speaks of the situation at Lymanhurst in Minneapolis, where there were estimated to be 20,000 children infected with tuberculosis and 70,000 others who needed protection from infection. The capacity for treatment at Lymanhurst was 175. Certainly the expenditure of funds for the care of this small number in view of the much larger problem accomplished very little.

Consequently, the money formerly used to maintain these children in the preventorium unit is now employed to do tuberculin testing on large groups of children; to search out and segregate the source of contamination of the positive reactors, thus making not only the child in his own home safe, but also giving protection to the rest of the community; and finally to follow up the adolescent positive reactors by frequent x-ray examinations in order to detect the reinfection form of tuberculosis sufficiently early to institute therapeutic measures aimed at arrest of the process and prevention of the victim's in turn becoming a spreader of bacilli. Such a program would seem to yield far greater returns, in terms of tuberculosis control, for the financial outlay involved, than the preventorium method. According to Stewart,[4] similar changes to those going on at Lymanhurst are now in process of development elsewhere.

Pastor,[5] in discussing the fight against tuberculosis in Puerto Rico, advances further arguments against the value of the preventorium in his locality. He found it cost as much to maintain a well child in a preventorium as to support a tuberculous patient in a sanatorium. Taking the child away from the home to protect him from contagion is an expensive and impractical procedure. It is far easier, more effective, and less costly to send away the focus of contagion, leaving the rest of the family at home. Beds in sanatoriums should be for sick persons who are potential sources of contamination. He suggests that tuberculosis workers adopt the slogan, "Make every home a preventorium."

Moreover, if protection of the infected child is to be effective, it must not be limited to a few months of institutional care, where the child merely gains a few pounds of weight only to lose it when he returns to his poor home, but it must extend over a period of years into adult life, since most childhood infections that do light up do not become activated until the age of puberty or thereafter. "By keeping the home free from foci of contagion, raising its standards, educating parents, and affording facilities for systematic clinical supervision of contacts, we could probably achieve more in the prevention of tuberculosis than has been achieved by all the preventoria of the past and of the present," says Pastor.

Hawes,[6] on the other hand, is convinced that properly run preventoriums and summer camps are decidedly worth while in the campaign against tuberculosis. On the basis of fifteen years' experience with the Prendergast preventorium in Boston, he states that he knows "of no more effective way in which our present knowledge of tuberculosis may be extended than by means of the preventorium and the summer camp, providing that active and practical measures are used to educate not only the children themselves in the principles of health and hygiene, but also their parents and other members of their families, and likewise the general public, including physicians, nurses, and social workers, as well as the laity." As proof of the value of the work that may be done in a preventorium like Prendergast, he compares 705 children admitted to that institution in the decade from 1922 to 1932, with 705 other children with similar tuberculosis experience who had not been to Prendergast but had been taken care of in their homes either by family physicians or doctors and nurses from a health clinic. In the Prendergast group of children it was found that only one had subsequently died of tuberculosis, and only three had developed the disease in clinical form, whereas in the other group ten had died from tuberculosis and forty had developed the disease.

The figures presented by Hawes represent a striking difference in morbidity and mortality in favor of the preventorium group of children. One is inclined to think the efforts of breaking contact in the nonpreventorium group could not have been very effective. However, if further observation of comparable groups continues to show similar results, then certainly a powerful argument exists justifying preventorium residence.

CONCEPTS OF TUBERCULOSIS

Fifteen years of longitudinal study of many thousands of children for tuberculosis have enabled the Lymanhurst workers to form a concept of the evolutionary course of tuberculosis as it occurs in the human being from the beginning of the first seeding of tubercle bacilli on normal preallergic tissues to disabling disease or death from chronic destructive pulmonary tuberculosis. Their observations have been presented so succinctly and so convincingly that probably the rank and file of physicians in this country are in agreement with their views. However, there is a substantial number of other well-known workers in the tuberculosis field, whose opinions command respect, who differ with some of the interpretations of the Lymanhurst group. Controversial questions center largely about the significance of allergy and immunity; about racial and individual resistance; about the reason for the infrequent appearance of phthisis before the age of ten; about the effect of the massiveness of the infecting dose of organisms; about the relative importance of endogenous and exogenous sources in causing reinfections; about the part played by a first infection in preventing or predisposing to later reinfection types of tuberculosis; and finally about whether it is more desirable to enter adolescent and adult years with a negative or with a positive reaction to tuberculin.

The impression should not be gained that these are the only problems remaining for solution in tuberculosis, but merely, that at the present time, they are the questions receiving most attention in the literature on tuberculosis in children.

In last year's review[7] the Lymanhurst interpretation of tuberculosis was presented in considerable detail. It may be advantageous to restate the high points of that concept here, to add further contributions which have been made during the year, and then to consider some of the views which approach the problem from other angles.

Recent articles by Myers and his associates[8] and by Stewart[4, 9] summarize their ideas on the evolutionary course of tuberculosis. According to these authors, there are two general types of tuberculosis, the first infection type and the reinfection type, both caused by the same organism, but differing so markedly in almost every other respect as to suggest they are separate disease entities. Concerning this statement there is almost universal agreement among tuberculosis workers, but it may be said to be unique in this respect.

First infection tuberculosis results when tubercle bacilli are seeded on nonallergic tissues, whereas reinfection type tuberculosis requires for its development that the tissues be allergic to tuberculoprotein when the bacilli are implanted. The one essential determining difference between the two types, therefore, is allergy, and this holds true regardless of the age of the patient as will be brought out later. First infection may occur in the lungs, abdomen, or cervical region, and the foci may be single or multiple, large or small. It is probable, too, that from the primary focus during the preallergic period bacilli are disseminated like particulate matter to various organs of the body thus setting up numerous other foci which may be of importance in the development of subsequent reinfection forms of tuberculosis. Proof is not available, but it is possible that this is the mechanism involved in the formation of the foci in the brain, from which bacilli escape to produce meningitis as has been shown by Rich and McCordock. Similarly, it is conceivable that bone and joint tuberculosis or renal tuberculosis may arise from hematogenous "rests" deposited in these structures at the time of the primary infection, which do not become activated for months or years afterward.

During the preallergic stage following the initial infection, symptoms and physical signs are completely absent, and diagnosis of the condition is impossible except by recovery of organisms by gastric lavage. However, Myers states that he is at present engaged in a study to determine whether or not there occurs in the peripheral blood sufficient of the leucocytic, monocytic, and lymphocytic activity occasioned by tubercle formation to be of diagnostic significance. The difficulty in knowing the exact time infection takes place in accidental exposures obviously stands in the way of the practicability of this means of early diagnosis.

In from three to seven weeks sensitivity develops, and coinciding with it perifocal allergic reactions may occur about some favorably situated primary pulmonary lesions so that they can be visualized in x-ray films. Many of these lesions acquire central areas of caseation at the time allergy appears, and a transitory fever of varying intensity and duration may occur during this period. However, only a small percentage of the children who become infected with tubercle bacilli for the first time develop lesions which are large enough to cast shadows in the x-ray film. In those who do develop such lesions it is believed that the defense mechanism of the body has not adequately surrounded the foci of bacilli before allergy appears, thus permitting

a diffusion of tuberculoprotein into adjacent tissues which causes the collateral inflammation visible roentgenologically. In the majority of cases the defense mechanism is adequate, and no collateral inflammation occurs about the primary focus, which fact explains why the x-ray film is negative in such a high percentage of positive reactors. Cases of both types have been followed by serial x-ray study, and in both, at some subsequent time, calcium deposits have been observed to make their appearance.

To date 210 children with proved first infection tuberculosis (131 with pulmonary infiltration demonstrable roentgenologically) have been observed by the Lymanhurst group, and have been followed by serial x-ray study. One of these children died of tuberculous meningitis approximately a year after he had been sent to a first class sanatorium. All the others followed a surprisingly uniform course. For weeks or months no gross change occurred in the extent of the pulmonary infiltration. There then occurred a gradual progressive process of resolution which led in the course of months to two or three years, to a complete roentgenologic disappearance of the lesions, or to their reduction to trivial fibrosed scars or to calcium deposits. "The changes observed in these lesions," says Stewart, "illustrate on a large scale the evolution of all primary varieties of the disease, regardless of where the pathology is situated and irrespective of whether the lesions are large or small." Furthermore, this same course has been observed to follow when first infections have occurred in adults, thus disproving, in the opinion of the Lymanhurst authors, the popular belief that an adult who becomes infected for the first time nearly always develops rapidly progressive clinical tuberculosis. Also negro, Mexican, and Indian children have been observed who have resolved their first infections in the same manner as white children. This ability on the part of children of these races throws doubt upon the alleged destructiveness of primary infections in the adult members of such races. Such destructive forms are more likely to be reinfections.

In the centers of the calcareous foci virulent tubercle bacilli may remain alive throughout the lifetime of the individual, thus accounting for persisting sensitivity. Attempts on the part of nature to remove the calcified areas as foreign bodies by ossification and revascularization provide an opportunity for the freed bacilli to gain access to the blood stream, and hence to the potential establishment of reinfection forms of tuberculosis of endogenous origin.

According to the Lymanhurst interpretation, the term "reinfection type of tuberculosis" is applied to those forms of tuberculosis which develop as new lesions or which extend beyond the limits of the original primary pathology when such lesions develop after tuberculin sensitivity has become established, regardless of whether the complications occur a few weeks or many months after the first infection form of the disease was acquired. Thus tuberculous meningitis, miliary tuberculosis, tuberculous pleurisy with effusion, and bone and joint tuberculosis, as well as phthisis are all regarded as reinfection forms of the disease.

First infection tuberculosis is considered to be a relatively benign disease, which almost invariably undergoes resolution without any special form of treatment, whereas reinfection tuberculosis accounts

for practically all of the serious disease manifestations and deaths. However, primary tuberculosis is not, in the opinion of these authors, a beneficial experience to the host in that it tends to create a degree of immunity against the later development of serious tuberculous disease. On the contrary, they consider it a double liability: first, because it is responsible for the production of allergy to tuberculoprotein which is an essential antecedent to the development of reinfection tuberculosis; and second, because its original foci may be the source of the bacillary metastasis which results in early or late, acute or chronic forms of reinfection tuberculosis. In substantiation of this viewpoint, they call attention to the failure of first infections to create immunity sufficient to protect against tuberculous meningitis, bone and joint tuberculosis, and miliary tuberculosis, and point out that an immunizing procedure for other communicable diseases which was equally ineffective would hardly be acceptable. Moreover, they have shown that phthisis is never the result of a first infection but is always the product of a reinfection. In a group of 131 children with pneumonic lesions of first infection type not one developed into phthisis, but in a group of 54 tuberculin-sensitive patients who developed reinfection pneumonic infiltrations years after they acquired their primary infections, the invariable outcome has been progressive disease typical of phthisis, resulting in death for a fourth of the group, and in advanced disease for some of the others.

First infection tuberculosis, then, in the Lymanhurst interpretation, is the introductory state of all clinical varieties of the disease. It not only fails as an immunizing force to protect against the subsequent acquisition of phthisis, but actually contributes the essential factor which makes possible its development. The prognosis as regards tuberculosis for patients who contract a first infection cannot be determined for many years. A few of them, but not nearly so many as was once thought, will develop acute forms of reinfection tuberculosis, such as meningitis, and miliary disease; a few will acquire tuberculosis of the bones and joints and of various viscera; and from 10 to 20 per cent of this group of tuberculin-sensitive children are destined later to develop chronic pulmonary tuberculosis either from endogenous or exogenous sources. A positive tuberculin reaction, then, in the opinion of the Lymanhurst workers, can only be considered as a distinct liability to the child entering the age group susceptible to phthisis. The conquest of tuberculosis for the human race is to be achieved through epidemiologic and preventive measures, as it has been for the bovine family, rather than by widespread tuberculariza-tion and survival of the fittest.

Attention may now be turned to a consideration of some of the contributions appearing in the literature of the past year which attempt to shed further light on why tuberculosis behaves as it does in human beings. Myers[10] draws upon the results obtained by numerous workers in animal experimentation to offer a reasonable explanation for the observed benignity of first infections. He refers to the work of Vorwald[11] who found that within an hour after the intravenous injection of virulent tubercle bacilli into rabbits polymorphonuclear leucocytes could be demonstrated in alveolar capillaries grouped about collections of tubercle bacilli, some of which had already been phagocytosed. Within three hours mononuclear exudate cells had

collected in the walls of the capillaries surrounding the bacillus-laden polymorphonuclear leucocytes, and within a few hours more the exudate cells had taken on the function of phagocytosing tubercle bacilli and disintegrating leucocytes. Typical tubercle formation was evident at the end of a day. At the end of a week the typical predominating cells were the mononuclears, some of which could be recognized as epithelioid cells. By the end of a month the tubercles were macroscopic in size. Lymphocytes and plasma cells were concentrated about the tubercles, and central caseation was observed in some of the tubercles in which tubercle bacilli were found free. "This focalization and walling off of bacteria before sensitization appears may be an important factor in making primary tuberculosis a benign disease," states Myers.

He cites the studies of Lemon and Montgomery,[12] who show that the tissues of rabbits at first react with a nonspecific form of inflammation to bovine tubercle bacilli injected into the pleural space, as though they were foreign bodies of particulate type. The fluid and cellular parts of the resultant effusion are promptly resorbed, carrying with them the particulate material, which has been phagocytosed, and depositing it in regional lymph nodes and in remote organs. This preallergic nonspecific reaction of tissues is further illustrated by the experiments of Lemon and Feldman,[13] who compared the tissue reactions produced when particles of silica and virulent avian tubercle bacilli were introduced into the trachea of different rabbits. The early cellular reactions which developed about the particles of silica were essentially the same as those which appeared about the tubercle bacilli. Later, however, with the advent of sensitivity and in response to growth and multiplication of bacilli, the type of inflammation became specific in the tuberculous animals. Myers refers to various other studies which demonstrate that the injection of virulent tubercle bacilli into animals previously rendered allergic to tuberculin is followed by a more rapid and severe type of inflammation than that which results from an initial injection. For instance, Long[14] has shown that small doses of tubercle bacilli and their products have no immediate effect upon the cells of the testes of normal guinea pigs. However, when equivalent doses of tubercle bacilli are injected into the testes of animals which have previously been sensitized, degeneration of the cells begins almost immediately. And again Stewart, Long, and Bradley,[15] and Holst[16] found that leucocytes from animals which had not been infected with tubercle bacilli were not harmed when they were brought in contact with tuberculin, whereas leucocytes from animals with tuberculosis were definitely damaged under the same treatment. Also Seibert[17] sensitized normal guinea pigs and showed that a high degree of sensitiveness conferred no immunity or increased resistance to tubercle bacilli. On the contrary, it seemed to hasten and extend the lesion and to be associated with much more extensive necrosis and caseation than is found in unsensitized animals.

The events leading to the development of sensitivity of tissues in animals (and the reaction in humans is believed similar) following an initial infection with tubercle bacilli are described by Myers. "The first defense is offered by the neutrophiles when they phagocytose the tubercle bacilli in the blood stream. However, this defense is soon overcome, probably because of tuberculopolysaccharid which is toxic

to neutrophiles. These sluggish or dead cells containing tubercle bacilli accumulate even to the point of completely obstructing some capillaries, thus focalizing tubercle bacilli. The next line of defense consists of monocytes which engulf the disintegrating neutrophiles, but a tuberculophosphatid apparently is partially responsible for the early conversion of the monocytes into epithelioid cells. Although some tubercle bacilli apparently are killed by the epithelioid cells, others not only live, but also multiply. From the dead and disintegrating bacilli, as well as from those proliferating, more products are given off which stimulate the local cells. The waxes cause a proliferation of fibroblasts, and the acetone-soluble fat stimulates proliferation of all connective tissue cells. In due time, tuberculoprotein results in an outpouring of plasma about the lesion and later causes sensitization of the body to such an extent that it can be detected by the tuberculin test."

Thus, animal experimentation has been employed to show that a quick "walling off" of tubercle bacilli occurs following first infection, that no differentiation is made in tissue reaction between inanimate particulate material and tubercle bacilli until sensitivity occurs, and that tissue sensitivity is responsible for the development of specific destructive lesions. Correlating these findings with observations made on human beings Myers states, "The entire early development of tuberculosis occurs in the human body without symptoms, abnormal physical signs, or x-ray findings. In many cases, apparently the tubercle becomes fibrosed, and no significant destruction of tissue occurs. In my observations on large numbers of students of nursing and medicine who developed the first infection type of tuberculosis after exposure to patients, I have never seen one who presented any symptoms before the tissues were sensitized. Moreover, I have seen none who presented symptoms subsequently except those who developed reinfection tuberculosis, such as pleurisy with effusion, peritonitis, destructive pulmonary disease, etc."

Burke[18, 19] records an interesting study in animal experimentation, in which he produced primary and reinfection types of tuberculosis in rabbits and studied the resulting lesions by serial roentgenology, by roentgenograms of the excised lungs, and by pathologic examination.

The primary pulmonary tuberculosis produced in rabbits by the intratracheal injection of 1 mg. of virulent tubercle bacilli was comparable in many ways to primary pulmonary tuberculosis in children. The animals, like children with this type of tuberculous infection, were not ill and had no fever during the early progressive phases of the disease. The first roentgenograms to reveal shadows were those taken between the tenth and seventeenth days. The largest shadows were usually observed in the second month. Some of the films failed to show any shadows after the first three months, and commonly films made during the third and fourth months showed fewer and smaller shadows. In other instances, the shadows became dense and discrete and, having reached this stage, changed little during a period of years.

Both the roentgenograms taken during life and those of excised lungs failed in many instances to portray a true picture of the extent and location of disease demonstrable at pathologic examination.

Examination of the lungs of rabbits killed in later periods gave the author an unusual opportunity to observe successive stages in the

healing of primary pulmonary tuberculosis. In seven of the twelve rabbits killed between the eighth month and fourth year the lungs and paratracheal lymph nodes showed no evidence of disease. Some of the lungs showed various stages in the healing of tuberculous lesions by resolution, fibrosis, and calcification. Cavities were found in the lungs of only five of the thirty-five animals killed between the end of the first month and the end of the fourth year. Caseous foci were observed to be small, differing in this respect from those seen in the animals with reinfection tuberculosis.

In the second part of his experiment Burke sensitized rabbits by injecting avirulent tubercle bacilli in the groin, and produced reinfection tuberculosis by subsequent injections of 1 mg. of virulent tubercle bacilli. The disease thus produced was comparable in many ways to the adult type of reinfection tuberculosis seen in man. Unlike the rabbits with primary pulmonary tuberculosis, these became ill for a week or two following the injections, and many had fever. Abnormal shadows were found in the roentgenograms as early as the first day, and usually reached their largest proportions during the second week. However, no shadow or combination of shadows was found in the chest roentgenograms or in the roentgenograms of the excised lungs which served to differentiate the lesions of reinfection from primary. Caseous foci were larger, and more cavities were found in the lungs of the killed rabbits with reinfection experimental tuberculosis than in the animals with primary tuberculosis.

The author concluded that the study demonstrated a striking similarity between primary and reinfection types of tuberculosis produced experimentally in animals by a measured dose of organisms and the same types of tuberculosis as they occur in human beings.

Another approach to the acquisition of further information concerning the pathogenesis of tuberculosis is advanced by Sweany,[20, 21] who has made an extensive study of tuberculous calcifications. According to this author, primary calcifications can be differentiated from reinfection calcifications by the fact that, in general, the former are more heavily encapsulated and show a much greater tendency to ossification. Moreover, transitions from one type to the other occur with the development of allergy.

As a result of a study of multiple calcifications selected from over 600 autopsies, Sweany[21] concludes that "calcifications may result from any type of encapsulated tuberculous focus; namely, multiple primary seedings, scattered foci occurring in a resolving benign type of tuberculous pneumonia, in a hematogenous seeding occurring in the acute allergic period of the secondary stage of the primary, in various transition types from the primary into reinfection, in hematogenous reinfection, and in the healing of any form of tuberculous nodule or infiltrate arising from bronchogenic spread.

"By correlating the history, antemortem and postmortem roentgenographic findings, and the pathologic changes in multiple calcified lesions, it is possible in many cases to determine not only the character of the lesions themselves, but also attain an idea of the mechanism of the process leading up to their formation."

Frequent reference has been made in the literature to the report published by Heimbeck[22] in 1928 that clinical pulmonary tuberculosis developed much more frequently among nurses who entered training

on a tuberculosis ward in Oslo with a negative reaction to tuberculin, than occurred among those whose test was positive. This was interpreted as indicating that the nurses with the positive reactions were, as a group, more immune to tuberculosis than the negative group. Also, it is, or rather was until recently, the general impression that the acquisition of a tuberculous infection for the first time in adult life was likely to result in a severe form unusually resistant to treatment.

Myers' observations[23] on the development of tuberculosis among students of nursing and of medicine in the city of Minneapolis is of particular interest, therefore, in the bearing it has on these views. The students were tested to tuberculin upon entrance to the school and were usually retested at intervals of not greater than six months, since positive reactions known to have developed in such a short time possess diagnostic value in differentiating first infection lesions from reinfections which appear in x-ray films. When the interval between testing is a year or longer, this significance of positive tests is lost. Both the students of nursing and of medicine had opportunities for exposure to open cases of tuberculosis in their routine hospital work, and not infrequently the time and source of contagion could be ascertained quite accurately.

The individuals comprising the study are divided into six groups, on the basis of tuberculin reactions, and the type of lesions subsequently developed. Protocols are given for each patient.

Group 1 consists of two persons whose tuberculin reactions changed from negative to positive under observation and in whom erythema nodosum appeared.

In Group 2 are placed twenty-one persons whose tuberculin reaction changed from negative to positive and who developed a primary focus demonstrable by x-ray film examination. No other lesion was demonstrated. This is a significant group. They are adults never before infected with tuberculosis, but when they did become infected the resultant lesions were observed to run the same benign course as similar lesions which develop in infants and children. Over a period of time resolution went on to complete disappearance of the x-ray shadow or was reduced to fibrous strands or lime deposits. Symptoms were absent in the majority of these cases, and healing occurred without the employment of any special therapeutic measures. There was nothing characteristic about the x-ray shadows observed in these patients which served to differentiate between first and reinfection types of tuberculosis. (Compare with Burke's statement in experimental tuberculosis.) "It is only when one has carefully administered and interpreted tuberculin tests with sufficient frequency or has observed the lesions sufficiently long that such differentiation is possible," says Myers.

Group 3 is made up of nineteen cases whose tuberculin reaction changed from negative to positive and in whom primary parenchymal lesions were demonstrable by x-ray in some, and nondemonstrable in others. Pleural effusion also developed. This complication is looked upon by the author as a reinfection form of tuberculosis. The primary lesion sensitizes the tissues, and bacilli are transmitted to the visceral lymph channels from the lesion which frequently lies close to

the surface of the lung. While pleurisy with effusion occurs occasionally in infants and children who have acquired a recent first infection, it apparently is more common in young adults.

Group 4 consists of twenty-five individuals whose tuberculin reaction changed from negative to positive and in whom clinical pulmonary tuberculosis later made its appearance, with or without demonstrable primary focus or pleurisy with effusion. Three of these patients have died from tuberculosis. In each of them the evolutionary course of the disease was followed from exposure to tuberculous patients to death with resultant lesions. The other patients have been treated by modern methods, and most of them have their lesions at least temporarily under control.

This is the group which, according to views once popular, should have developed severe and rapidly fatal tuberculosis. "However," states Myers, "their lesions are no more severe and respond just as well to treatment as the lesions which develop in adult life among persons who were infected in infancy or childhood."

In Group 5 are included 15 individuals whose tuberculin reactions were positive when observation began, but in whom no evidence of clinical tuberculosis could be demonstrated. Later reinfection forms of tuberculosis made their appearance. In this group, then, a positive tuberculin test, indicative of previous tuberculous infection, did not produce sufficient immunity to prevent the development of clinical tuberculosis when exposure to tuberculous patients occurred. "Moreover," says Myers, "as far as we have been able to observe, the lesions which this group developed have not differed in intensity or in response to treatment from those who developed clinical disease after having become positive to the tuberculin test while under our observation."

Group 6 consists of four persons who had had no previous tuberculin tests, but negative x-ray films. All of them later developed extensive pulmonary tuberculosis. These patients are included in answer to the statement sometimes made that during the teen-age period x-ray films of the chest will reveal evidence of any disease which may cause illness at a later time in life.

Among the conclusions which may justifiably be drawn from this excellent piece of work are:

1. First infection type of tuberculosis possesses the same benign characteristics whether it occurs in infancy and childhood or in adult life.

2. The evolutionary course of tuberculosis is the same whether the first infection takes place in childhood or is delayed to adult life. A certain number will be followed by reinfection types of tuberculosis in either event.

3. The differentiation of pulmonary first infection and reinfection types of tuberculosis in adults depends upon one's knowledge of how recently sensitivity to tuberculin was acquired or upon long-continued x-ray study of lesions, unless symptoms characteristic of the reinfection form make their appearance.

4. Chronic pulmonary tuberculosis acquired by adults who have not been infected in childhood is no more severe or less resistant to treatment than is pulmonary tuberculosis which develops in adult individuals who have had positive tuberculin tests since childhood.

In the above paragraphs the attempt has been made to present a concept of the evolutionary course of tuberculosis from its earliest beginning when leucocytes phagocytose tubercle bacilli in the capillaries to the development of the chronic reinfection form of tuberculosis and to include the essential evidence upon which such a concept is based. There remains now the necessity of recording some of the published opinions of those who hold other views.

First of all, attention may be directed to the recently expressed opinions of Wallgren,[24] of Gothenburg, Sweden, an author who has had an extensive experience with tuberculosis. Concerning the much debated question as to whether a first or primary infection equips the host with sufficient specific immunity to prevent the subsequent development of pulmonary tuberculosis, he advances the interesting theory that there are, or can be, two distinct types of immunity: one against exogenous reinfections and the other against the infection which is already in the body and which has produced pathologic changes. An analogous situation is found in syphilis, in which the syphilitic individual is immune against reinfection, but, nevertheless, if untreated, may die as the result of progressive activity of his original infection. The immunity to exogenous reinfections in tuberculosis, however, is only relative, but sufficient under ordinary conditions to protect a tuberculin-positive child from appreciable risk, if the child is subjected to new possibilities of infection. Under unfavorable conditions this relative immunity may be broken through, and reinfection may take place. But against the virus of the primary infection and development of disease from its foci, there is no noteworthy specific immunity.

Another significant point raised by Wallgren has to do with the definition of the term "reinfection." It is incorrect, he believes, and has led to much confusion, to speak of reinfection tuberculosis as including dissemination of bacilli from primary foci in the postallergic period. He would abandon the term "endogenous reinfection" and would restrict the meaning of reinfection to apply only to exogenous, or new infections from without.

To the question, "Is it advantageous to have passed through a primary infection?" he answers, "Yes and no." Were it possible throughout life to avoid with certainty the risk of virulent infection, then naturally, this would be best, for in this way could be avoided all tuberculous disease, including consumption. But obviously at present this ideal is not attainable, at least for the average city resident. It is, therefore, necessary to weigh the advantages of a first infection in childhood against its disadvantages.

The outstanding advantage of a successfully undergone primary infection is the relative specific immunity secured against exogenous reinfection pulmonary tuberculosis. But in the acquiring of the primary infection and for several months immediately following, particularly for young children, there is created a serious risk with reference to inception of tuberculous meningitis, miliary tuberculosis, pleuritis, and tuberculous peritonitis, all of which conditions are directly related to the primary infection. "Therefore," says Wallgren, "no one would in cold blood expose a previously noninfected child to a virulent tuberculous infection merely to let the child benefit later from the specific relative immunity which the primary infection creates.

The risks are too great. For this purpose there is, on the other hand, no risk in using Calmette vaccine, although the immunizing effect of this can possibly never be thought to compare with that of the virulent primary infection." But the child who is safely past the risk period must be considered to be in a more advantageous position from this standpoint than the child who has just been infected or who has not been infected at all. The point is illustrated by comparing a group of tuberculin-positive children with a group who are tuberculin-negative, all exposed to a consumptive teacher in a classroom. Nothing happens to the tuberculin-positive group, but some of the tuberculin-negative group will become ill, and one or more may succumb to meningitis or miliary disease.

If it be granted that the tuberculin-positive child has a degree of specific immunity toward exogenous reinfection and that he is past the risk period of meningitis, miliary disease, etc., there is yet a disadvantage arising out of the primary infection which merits serious consideration. In Wallgren's conception of the genesis of lung tuberculosis, he postulates the hematogenous dissemination of tubercle bacilli to various organs in the body very early in the course of the primary infection. Thus foci may be set up in the bones, joints, kidneys, peritoneum, pleura, and in the lungs at a point apart from the primary focus itself. Such foci create little or no tissue reaction, and they may remain in a state of latency until some special set of circumstances causes their activation. Tuberculosis of the bones and joints is generally understood to originate in this manner. And it is Wallgren's contention that pulmonary tuberculosis, or phthisis, not occasionally, but usually, is brought about in the same way. He says, "Tuberculosis of the lungs according to this concept is usually not the immediate result of introduction of tubercle bacilli either from the outside or the inside into the allergic portion of the lung, but is rather the effect of activity by tubercle bacilli, which in most cases of lung tuberculosis have long remained in the same place, but have not been able to start a progressive process on account of resistance on the part of the organism and especially the lungs."

Finally, he discusses the problem of why only 1 or 2 per cent of the general population develop pulmonary tuberculosis, and why it does not commonly make its appearance until the age of puberty has been reached. Neither variations in virulency nor dosage of organisms are responsible. Therefore, it must be due to variations in resistance in the infected organism and especially in the infected tissue that make it possible for some individuals to contract lung tuberculosis while others do not. The well-known fact that phthisis seldom occurs in children before the age of puberty suggests that allergy cannot be the sole factor responsible for the bringing about of lung tuberculosis, for the chances are that children who have been infected at an early age and thus have become allergic meet with reinfection as often as individuals in and above the age of puberty. That puberty shall have been reached, then, seems to be one of the essential requirements, and this in turn is probably intimately related to internal secretions. The most significant factor, according to Wallgren, however, in order that lung tuberculosis shall develop from a primary infection, is probably hereditary disposition. Resistance-reducing factors such as unhygienic living, infections, and diseases, are important, but are second-

ary. "The first prerequisite that a lung tuberculosis shall develop is a tuberculous infection and this regardless of whether the infection occurs during childhood or later. The second prerequisite that lung tuberculosis shall develop is a disposition, and among all the constitutional and conditional factors, which together constitute the concept of disposition to consumption, the most significant are heredity and that the age of puberty shall have been reached," states Wallgren.

Opie[25] expresses still a different conception of the pathogenesis of tuberculosis from either that of Wallgren or of the Lymanhurst group. He regards first infection as a progressive disease, starting with an area of tuberculous pneumonia somewhere in the lung, progressing to adjacent lymph nodes, disseminating of tubercle bacilli by way of the blood stream to distant organs, as the spleen, liver, and meninges, and leading in many instances to death from generalized miliary tuberculosis. All of these ramifications are part of, and characteristic of, the first infection. In infancy it is accompanied by a relatively high mortality rate, but is usually benign throughout childhood. Adult negroes often exhibit the essential features of first infection tuberculosis as it is seen in white infants.

The type of tuberculosis which develops in adolescence and adult life is entirely different from the first infection type and is not, in his opinion, a continuation of the first infection, but is a new exogenous reinfection. However, its localization in the lung and its chronicity are referable to the immunity conferred by the first infection. Anatomic studies have repeatedly shown that at the time when the infection of adult life is progressive, the lesion of first infection is encapsulated and healed and there is no evidence that the former spreads from the latter. In a comprehensive study of the spread of tuberculosis in a thousand families Opie[26] and his associates have shown that in white persons first exposed to tuberculosis after fifteen years of age, pulmonary tuberculosis with few exceptions has the characteristics of the adult or reinfection type of the disease. The marked increase in mortality rate over that of the general population occurring in persons over fifteen years of age exposed to open cases of tuberculosis is further evidence of its exogenous origin. Furthermore, recent roentgenographic study of married couples has given proof of the transfer of tuberculosis of the lungs from one to the other partner in nearly half the cases. Since this is a far greater rate than occurs in the general population, it can only be interpreted as indicating exogenous infection. Also, it was apparent in the study referred to above, that the severity of the disease in adolescents and adults as well as in children, varied, being more severe in the individuals exposed to open cases of tuberculosis than in those exposed to tuberculosis in which no dissemination of tubercle bacilli was demonstrable. Such variation is explainable on the basis of variation in the number of tubercle bacilli in the environment, which again shows that pulmonary tuberculosis is an exogenous infection.

It is apparent, therefore, that no unanimity of opinion concerning the pathogenesis of tuberculosis exists even among competent observers of wide experience. The lesions of first infection to one (Opie) become a closed chapter and, except for the immunity produced, bear no relation to the development of phthisis in adolescent and adult life. Phthisis results only from an exogenous infection, and only in

those individuals in whom the massiveness of the infecting dose overcomes the immunity imparted by the first infection. To another (Wallgren) phthisis seldom if ever results from an exogenous infection. The immunity set up by the first infection prevents outside reinfection. Phthisis results from an activation of tubercle bacilli planted in the lung usually years before, when hematogenous dissemination of organisms from the primary focus took place. In a third interpretation (Lymanhurst) phthisis may be the result of either an endogenous or an exogenous reinfection. For its development it is essential that there has been a preexisting first infection which has sensitized the tissues to tuberculoprotein. The immunity feature of the first infection is negligible.

No conclusions as to which of these concepts expresses the true situation is possible. The literature of the past year contains many excellent discussions bearing upon this interesting phase of tuberculosis which have not been recorded here because of space limitation. To those interested, however, reference may be made to articles by Miller and Rappaport,[27] by Pinner,[28] and by Long.[29]

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Proceedings

SIXTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

KANSAS CITY, MO., MAY 11 AND 12, 1936

Round Table Discussion on Recent Advances in Nutrition

Chairman: Dr. W. McKim Marriott, St. Louis.
Assistants: Dr. Samuel W. Clausen, Rochester, N. Y.
Dr. Philip C. Jeans, Iowa City, Iowa.

CHAIRMAN MARRIOTT.—The aim of the nutritionist is to provide in utilizable form those materials which are necessary for the building up and maintenance of a bodily structure which will be functionally adequate. This aim may, to a considerable extent, be frustrated by such factors as heredity, congenital anomalies, or disease.

As the pediatrician deals with the body during the growing period, he may be compared with the builder of edifices; the internist and the surgeon, with the repair men. Given a solidly constructed structure, it will last well, and the minimum of repair work will be required. We cannot alter the general plans of the architect, but we can see that the proper materials go into the construction. Two buildings of the same size and outward appearance may differ greatly, depending upon the care taken in construction; the one may approach perfection in structure and wear well, the other, because of the use of poor materials, will not withstand wear and tear. It is so with the child's body; the architectural plan of nature may be excellent, but with skimping on materials a poor structure may result.

Adequate nutrition implies far more than the attainment and maintenance of a certain body size and weight or a certain thickness of adipose tissue. A child may be of average stature for the age and have an average height-weight ratio, yet the nutrition cannot be considered as satisfactory if the child is anemic, has weak flabby musculature, poor posture, hypoplastic or carious teeth, or a colloid goiter, or if he suffers from atonic constipation or night blindness, has but little resistance to infection, and is incapable of sustained physical or mental effort.

The growing body must be supplied with the necessary building materials to perfect its structure and to provide adequately for functional activity. If the total fuel or caloric value of the food is inadequate to provide for the energy exchange, the laying down of body tissues is of necessity interfered with, or else tissues already formed are destroyed to meet the energy demands. On the other hand, with an entirely sufficient caloric intake but insufficient protein and mineral salts, muscle, blood, and bone development may fail to keep pace with weight gain. Without sufficient mineral salts, protein cannot be laid down as active protoplasmic tissue. When vitamin D is lacking, calcium and phosphorus may not be deposited as normal bone structure even though these elements are supplied in liberal amounts. When the diet is deficient in carbohydrate, the processes of metabolism are deranged with the ac-

cumulation of potentially harmful ketone bodies. Even an abundant intake of all known dietary essentials may not result in normal nutrition unless a certain balance is preserved. Thus with what would ordinarily be an adequate calcium supply, a great excess of phosphorus in the diet may interfere with the utilization of calcium, and a great excess of calcium may interfere with the utilization of iron, and vice versa.

Even after normal body structures have been formed, these may suffer functional impairment due to lack of certain essentials in the diet. For example, epithelial structures become keratinized and readily invaded by bacteria when vitamin A is deficient; the gastrointestinal tract becomes atonic and the appetite is lost when vitamin B is deficient.

The digestibility of the food must of course be considered, especially in the case of infants. In dealing with children, psychic factors must necessarily be taken into consideration. A balanced diet which may be relished by the laboratory rat may be refused by the child.

It is often stated that the instinct serves as a fairly reliable guide in the selection of foods, and examples are cited of primitive peoples with no knowledge of nutrition who instinctively choose well-balanced diets and even of young children who, given free selection, choose diets which meet their nutritional requirements. While, in general, the instinct may lead the individual to select a complete diet, this cannot always be relied upon. All primitive peoples are not well nourished, and, unless a very wide choice of foods is readily available, certain essentials may be omitted, and the diet as a whole may be poorly balanced.

The appetite serves, in general, as a good guide to the total amount of food needed, and, provided a suitable dietary mixture is offered, there is but little danger of under- or overfeeding when the amount of food taken is regulated by the appetite of a normal infant or child. A child who has been underfed for a time will often take large amounts of food when given a free choice and gain at an extraordinary rate, but, as the nutrition improves and the weight approaches the norm for the age and the body build, the appetite falls off and the rate of gain becomes less. Normal infants and children, given all they wish to eat of a well-balanced diet, are not likely to become overnourished. It is true that infants fed on the more modern concentrated formulas and given about all that their appetites demand are, as a group, larger and heavier than the accepted averages. They are not excessively fat. The fact that they are larger and heavier and have retained more calcium, phosphorus and nitrogen is not to be interpreted as meaning that they are oversized or overfed. Such infants may be considered as approaching *ideal* body standards, which from the very nature of the case differ from *average* standards. It should be the aim of the pediatrician to have the child's nutrition approach the ideal rather than to keep it to the average.

It has been customary to consider the breast-fed infant as the ideal and breast milk as the only perfect food; yet all breast milk is not perfect; nor do all mothers have a sufficient amount for their offspring. Breast milk is subject to greater daily variations than mixed herd cow's milk. There may be alterations in the total amount and in the calcium, fat, and vitamin contents, depending upon the mother's diet and living conditions. Breast milk, although adequate for the normal infant, does not contain sufficient protein for the special requirements of the premature or undernourished infant. Infants who nurse at the breast are likely to take considerably larger volumes of food than those offered carefully measured amounts of a formula from a bottle and hence they grow more rapidly. Given a good cow's milk formula under sanitary conditions, the ultimate results may, by all standards, be as satisfactory as those obtained with breast feeding.

Certain individual constituents of the diet require special consideration. In the case of the infant and the growing child, there is an especially high requirement for

protein because of the laying down of new body tissue. The breast-fed infant receives about 10 per cent of the total calories in the form of protein, or approximately 2 gm. per kilogram of body weight. In the case of the infant receiving cow's milk, however, a larger amount of protein is needed because of its poorer nutritional value. A suitable allowance is 15 per cent of the total calories, or 3.5 gm. per kilogram of body weight per day. This corresponds to 1.5 oz. of cow's milk per pound of body weight per day. Infants receiving protein at higher levels grow somewhat more rapidly and have more solid tissues. A protein intake somewhat in excess of the average amounts mentioned above does little or no harm. The idea that moderately high protein feeding damages the kidneys of the human has failed of substantiation. A high protein diet does cause some hypertrophy of the kidneys but no pathologic changes. An insufficient amount of protein, on the other hand, results in slow growth and anemia. When the protein of the diet is low, the serum proteins are diminished in amount, and when, as the result of this, the colloidal osmotic pressure of the plasma falls below a certain level, nutritional edema of a greater or lesser degree occurs. As judged from clinical evidence, a low serum protein level is associated with decreased resistance to infection, possibly as the result of a lowering of the globulin fraction. Although animal proteins may more quantitatively be converted into body protein, satisfactory nutrition may be maintained through a proper selection of vegetable proteins; excellent results have been accomplished with the proteins of soy beans and of almonds. Some idea of the protein needs of the individual may be gained by consideration of the creatinine output. This phase of the subject will be discussed subsequently by Dr. Jeans.

The particular physical property of milk casein in forming curds during the processes of digestion has claimed a great deal of attention. One of the chief disadvantages of cow's milk for the feeding of the infant has been assumed to be the character of the casein, in that it forms large curds in the stomach. This particular disadvantage may be so easily obviated by heat treatment, acidification, or by other methods that it need not give us serious concern.

Fat is not as essential in the dietary as protein. Certain unsaturated fatty acids, such as linoleic acid, appear to be necessary for normal nutrition, but the amounts required are minimal. Linoleic acid may be considered in about the same category as the vitamins. Most natural fats carry small but adequate amounts of this fraction. The two important vitamins A and D are associated with the fats in natural foods. It is for these reasons that diets very low in fat are likely to be unsatisfactory unless especially supplemented so as to provide the essentials mentioned. In the average dietary about 35 per cent of the calories may to advantage be supplied by fat, but great variations in this amount may be made without noticeable effect on the nutrition. The most comprehensive study of the metabolism of fat, especially in infants, has been made by L. Emmett Holt, Jr., and associates.[1] They have shown that the size of the globules in milk has little or no influence on digestibility and that digestibility is more related to the structure of the fat than to its melting point. Special fat mixtures designed to replace butter fat were shown to possess no particular advantages. An interesting reciprocal relationship between fats and mineral constituents of the diets was demonstrated, an excess of fat resulting in loss of certain minerals from the system and an excess of certain minerals leading to diminished fat utilization.

Carbohydrate is the most economical food both from the financial and metabolic standpoints. With self-selection of diets by older children and adults, approximately 50 per cent of the calories are ordinarily taken in the form of carbohydrate, and of this about one-half is starch and the remainder sugar. In the case of the young

[1]Holt, L. Emmett, Jr., Tidwell, Herbert C., Kirk, Claude M., Cross, Dorothea M., and Neale, Sarah: Studies in Fat Metabolism: I. Fat Absorption in Normal Infants, J. Pediat. 6: 427, 1935.

infant, sugars are the sole source of carbohydrate until starch is fed. When cow's milk is used for infant feeding, it has been empirically determined that a suitable amount of added carbohydrate is between 5 and 10 per cent of the amount of milk. Taking as an average 8 per cent, this will mean one-half as many calories are added as carbohydrate as are furnished by the milk. Too little carbohydrate necessitates excessive intake of fat and protein. Too much carbohydrate, on the other hand, may result in insufficient intake of protein. An additional disadvantage of high carbohydrate feeding, particularly of sugar, is that of intestinal fermentation. Starch is more slowly digested and absorbed than sugar, hence does not flood the blood with glucose. As to the advantages and disadvantages of the individual sugars in infant feeding, experimental observations are conflicting. The normal infant appears to do about equally well when fed lactose, sucrose, or dextrin-maltose mixtures. Sucrose leads to more rapid gain in weight than lactose and to more fat formation than the dextrin-maltose mixtures. Lactose is rather slowly absorbed and tends to change the bacterial flora of the large intestine to a type resembling that of the breast-fed infant. There is some evidence that lactose feeding favors calcium absorption, possibly because of the formation of lactic acid in the lower portions of the intestinal tract. The monosaccharides, dextrose and levulose, are the most quickly absorbed of the sugars and require no digestive effort; they are, however, in concentrated solutions, more irritating than the disaccharides and much more so than dextrin. Dextrose and levulose are capable of absorption and utilization in patients with celiac disease who are unable to tolerate starch or the disaccharides.

The mineral constituents of the diet assume especial importance during the growing period. Adequate amounts of sodium, potassium, magnesium, sulphur, and chlorine are likely to be contained in any average diet, and it is not usually necessary to make additions of these elements. Calcium, phosphorus, iron, and iodine may, on the other hand, be deficient unless the diets are especially selected or these elements added in inorganic form. Calcium and phosphorus seem to be better absorbed when given in the form of milk than in any other form, but, in general, minerals may be as satisfactorily supplied as simple inorganic salts as in specially selected diets. There would appear to be very little reason for taking large amounts of foods containing a few milligrams of iron or iodine per pound when simple inorganic salts will supply every need. When cod liver oil is given to infants and children, a fair amount of iodine is supplied at the same time. Only a few natural foods contain significant amounts of iron, and the much vaunted spinach may when fed actually rob the body of iron. The metabolism of iron, of calcium, and of phosphorus will be discussed further in this symposium by Dr. Jeans.

The importance of the selection of foods providing an alkaline ash has been overrated. A diet having an ash approximating neutrality is perhaps the best, but a moderate variation on either the acid or alkaline side is practically without effect. Following severe diarrhea or vomiting, the acid-base balance may be greatly altered, and the same is true in the presence of diabetes or nephritis, but this does not concern us in considering the nutrition of the normal child.

Recent advances in our knowledge of the vitamins will be discussed by Dr. Jeans and Dr. Clausen and thus will not be referred to at this time.

The state of nutrition may be influenced not only by the diet but by intrinsic body factors, such as heredity and the interrelationship of the various endocrine hormones, especially insulin, epinephrine, thyroxin, and numerous pituitary hormones. A detailed consideration of these would be beyond the scope of the present discussion.

It is not to be assumed that all factors influencing nutrition are as yet known. Certain foods, especially fruits, seem to have somewhat specific effects which it is difficult to explain on the basis of what we know of the individual factors present. The severe digestive and nutritional disturbance known as celiac disease is still obscure so far as etiologic factors are concerned, yet it may be controlled by dietary means.

The discussion as related to certain specific factors in nutrition will be continued by Dr. Jeans.

Specific Factors in Nutrition

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Nitrogen Metabolism and Muscle Growth

At the time of birth and throughout the first year of life muscle tissue, according to Scammon, comprises approximately 25 per cent of the total body mass; at twelve years of age and thereafter the proportion is 40 per cent. Thus the muscle tissue undergoes not only an absolute, but also a relative, increase in relation to the remainder of the body. The time at which the relative increase occurs has not been determined.

It has long been known that creatinine excretion is proportionate to muscle mass. A study of creatinine excretion at various age levels should give information concerning the age period at which the relative increase in muscle mass occurs. It has been found that the creatinine excretion of the breast-fed baby is approximately 10 mg. per kilogram and that of the artificially fed baby who is receiving an abundance of food is 12 to 13 mg. per kilogram. The level of creatinine excretion per kilogram for the adult is approximately the same as that for the child of twelve years, viz., 20 mg. per kilogram. When the creatinine excretion per kilogram is determined at various age levels, it is found that the values remain practically constant until the age of three years. At approximately three years of age the values rise rapidly. This rapid rise continues until about nine years. After nine years of age the curve of increase becomes much less steep and before twelve years of age reaches the maximum level which is maintained thereafter. From these observations it may be concluded that the period of most rapid muscle increase in relation to the body mass occurs between three and nine years of age.

In the first year of life the relative amounts of creatinine excreted indicate that the artificially fed baby who is receiving ample food has a more rapid muscle growth than the breast-fed baby. The proportion of muscle weight to total body weight, though greater than that of the breast-fed baby, is maintained at a constant ratio throughout infancy.

This discussion has considered only the changes in muscle mass in relation to its proportion of the total mass of the body. Total growth is rapid in infancy and slows very definitely before three years of age, when the changed relationship between muscle and the remainder of the body begins. The absolute increases in muscle tissue are reflected in the nitrogen retentions. During the period of rapid growth in the first year, approximately 27 per cent of the ingested nitrogen is retained. From the age of one to three years, with the same nitrogen intake, the retention is only one-third of this value, representing a definite slowing in the speed of total growth, while at the same time the muscle mass remains the same proportion of the total body weight. Between four and nine years, while the muscle mass is increasing out of proportion to the total body weight, from 14 to 15 per cent of the ingested nitrogen is retained, even though the rate of total growth is less than it is between one and three years. After nine years of age the percentage of nitrogen retained again decreases. Thus the nitrogen retentions offer further evidence that the period of greatest relative increase in muscle is between three and nine years of age.

Many physicians are disturbed over the apparent loss of appetite between one and three years of age. Regardless of intake, children at this age retain less calcium, phosphorus, and nitrogen than at any other age period from birth to twelve years. From these facts it may be interpreted that the lessened food intake is physiologic and is not to be considered abnormal. The evidence seems equally clear that children from three to nine years of age need a high protein diet as much as do those in the period of adolescence.

Effect of Sugars on Calcium and Phosphorus Utilization

Animal experiments have indicated that conditions in the intestinal tract are much more favorable for the absorption of calcium and phosphorus when the food contains lactose than when it contains other sugars commonly used in infant feeding. On the basis of these experimental results many have assumed that in the artificial feeding of infants lactose would have the same favorable influence. The animal experiments were conducted with a relatively low intake of calcium and phosphorus, whereas the observations on infants have been made with a relatively high intake of these substances. The formulas consisted of undiluted milk with 6 per cent added sugar. With calcium and phosphorus retentions used as the criterion, no difference could be detected between the results with lactose and those with dextrin-maltose preparations. The same calcium retentions were observed with corn syrup as with the dry dextrin-maltose preparations. However, when dextrose was the added sugar in the formulas for infants under five months of age, the retentions were slightly but significantly lower than with the other sugars mentioned.

From a group of infants from eight to thirteen months of age whose retentions had been under continuous observation previously, those were chosen who had the lowest retention values. For this group of selected infants lactose was substituted in the formula for the dextrin-maltose mixture previously used. In the thirteen studies made, no increase in retentions was observed as a result of the substitution. It is possible that some difference might have been found had the amount of milk been less or the amount of added sugar greater, but the proportions used were those commonly employed in infant feeding.

From these observations it may be concluded that no significant difference is to be observed in calcium retentions when comparison is made between feeding formulas containing lactose and those containing dextrin-maltose mixtures when the formula consists of undiluted milk with 6 per cent added sugar. Under these same conditions the use of dextrose as the added sugar apparently permits significantly smaller calcium retentions than those obtained with the other sugars mentioned.

Dextrose in Malnutrition

In the condition known as celiac disease, a diet high in protein and in monosaccharides and low in fats and complex carbohydrates has proved uniformly successful. Since one of the prominent symptoms of children with celiac disease is malnutrition, it seemed possible that children with malnutrition from other causes might benefit from this same type of diet. When this idea was put to the test of trial, it was found that malnourished children utilize the celiac type of diet far more efficiently than either the average normal diet or one high in fat.

Children who were markedly underweight did not make consistently good gains on the average diet until the energy intake reached 50 calories per pound. At this level fair gains were made also with a diet high in fat, but these were not as satisfactory as those with the average diet. However, when the celiac type of diet was administered at the level of 50 calories per pound, the gains were very rapid, some children increasing their weight at the rate of a pound a day for considerable periods.

When the energy intake was maintained at approximately 35 calories per pound, children receiving the celiac type of diet made fair gains, whereas with the average diet and the high fat diet at this level no gain was observed. When malnourished children are receiving a high fat diet in sufficient quantity to permit gain in weight, a greater gain in weight will be observed if the energy intake is reduced by 500 calories and the celiac diet substituted for the high fat diet.

Certain fruits are relatively rich in monosaccharides. Equivalent amounts of these fruits may be substituted for dextrose in the celiac diet, and the results are the same. Substitution of bananas in this manner gave results identical with those de-

scribed for dextrose. In the celiac, or high dextrose, diet the amounts of dextrose varied from 250 gm. daily for a child of six or seven years to 500 gm. for a child of twelve or thirteen years.

It might be assumed that weight gains made as a result of a high sugar diet would consist largely of water. It is possible that this is true for the rapid gain of the first few days of the diet. However, metabolic observations have demonstrated conclusively that the net result is a substantial increase in useful tissue rather than water. This was indicated by the high retentions of nitrogen, calcium, and phosphorus and by the increased excretion of creatinine. It was observed that when the weight increased 20 per cent, the creatinine excretion increased 35 to 40 per cent.

These observations demonstrate that the malnourished child utilizes a high dextrose, low fat diet much better than the average normal diet and far better than a high fat diet. The same is true to a far greater degree with a child with celiac disease. It seems entirely possible that malnutrition itself may be an important determining factor in the production of celiac disease.

Malnourished children practically always are ingesting a diet which provides considerably less energy than the requirement. It is entirely logical to think of such a child in terms of a greater food intake. It may be logical also to think of cream and other fats as providing the additional energy in small bulk. With great frequency one finds that dietary increases have been advised along these lines. The observations of the preceding discussion demonstrate the fallacy of this type of advice. Much greater success will be attained with the high dextrose diet and at a lower energy intake.

Iron

The infant at the time of birth has a small store of iron. The amount varies greatly but does not average more than approximately 15 mg. or an amount which would be necessary for the formation of about 50 c.c. of blood. For approximately two months after birth a rapid destruction of hemoglobin occurs. As a result, from 150 to 200 mg. of iron is liberated. It is the general concept that all of this iron is stored for use in hemoglobin formation and that this amount is sufficient to supply the iron needs of the infant until six months of age. On a theoretical basis it is true that if all of this iron were conserved, the supply would be just sufficient for the needs up to six months. However, about 30 per cent of the iron freed from hemoglobin during the first two months is lost. During the period of hemoglobin destruction all infants are in negative iron balance. The diet supplies approximately 0.75 mg. of iron daily and the excretion varies from 1.5 to a high value of 4 mg. daily, producing an average negative balance of 1.35 mg. of iron daily. The stored remainder, equivalent to 300 to 375 c.c. of blood, would be sufficient to supply the iron needs until the age of about 4.5 months only if it were well conserved. However, babies receiving the usual milk formulas without additional iron are in negative iron balance during this period, and the reserve supply is exhausted before the theoretically calculated age. On this basis it becomes obvious that the diet of the infant requires consideration as regards iron considerably before six months of age.

The amount of hemoglobin present during infancy is less than at a later time. It is the general custom to consider this condition as normal. When statistical surveys are made and averages determined, these averages do not necessarily represent the normal. The finding of dental caries in 80 per cent of all school children would not be considered normal merely because it is an average of existing conditions. Elvehjem has found that, by giving an abundance of iron-containing foods to a selected group of infants, the average hemoglobin was more than 1 mg. to 100 c.c. greater throughout infancy than usual average values.

In order to maintain an infant in iron equilibrium, it has been found that the daily ingestion of 0.5 mg. per kilogram in the form of readily available iron is

necessary. It has been calculated that an average retention of 0.75 mg. daily is necessary to maintain normal hemoglobin formation. In order to attain this amount of retention, an average intake of 0.7 mg. per kilogram is necessary. These statements apply at all ages from seven weeks to one year of age. A general impression that babies under six months of age do not use ingested irons seems to be erroneous. Intakes of iron greater than 0.7 mg. per kilogram lead to greater retentions up to an intake of approximately 1 mg. per kilogram, above which amount little or no increase in retention is to be observed. Ingestion of iron in excess of this amount not only is without benefit, but may be actually harmful. It has been shown quite definitely for the chick that the feeding of iron in amounts comparable to the high dosages recommended at times by physicians for severe anemia produces within 1 to 2 weeks severe low phosphorus rickets, with death of all the chicks within three weeks.

On the basis of the preceding discussion the iron requirement of the infant may be met satisfactorily by the ingestion of 5 mg. daily from three to six months of age and 10 mg. daily from six to twelve months. These amounts will permit an average retention of 0.75 mg. daily, an amount calculated to be necessary.

Cow's milk varies greatly in its iron content, depending on the method of handling. As the milk comes from the cow, it contains approximately 0.2 mg. per liter. With transport in tinned iron containers it may acquire a content of 2.5 mg. per liter. The average of values obtained by six different observers is 0.6 mg. per liter. The usual milk formula of the artificially fed baby, including the customary orange juice supplement, may be relied upon to supply approximately 1 mg. of iron daily. If no other source of iron is made available, the infant will have a definite and often a marked deficiency by six months of age.

It is the custom of many to add egg yolk to the diet at the fourth month or even earlier. An egg yolk contributes approximately 1 mg. of iron. This amount in addition to the formula would still leave a deficit, even if the iron of the egg were all utilized. Balance experiments have shown, however, that the iron balance when egg yolk is fed is little different from that of the same diet without egg. The reason for this is not clear, unless it may be accounted for by the sulphur content.

Vegetables have had an extensive usage in infant feeding. One of the functions is to supply iron. They are often added to the diet at a relatively early age. It is necessary to concede to vegetables a certain usefulness. However, in the case of spinach we seem to have a product of overestimated value. Canned puréed spinach ready for use contains approximately 0.35 mg. of iron to the ounce. With a large serving of spinach the amount of iron obtained by an infant would be from 0.5 to 1 mg. This amount of iron would not contribute greatly to the total requirement even if it were all utilized. Balance experiments have shown that not only is the iron of spinach not utilized, but the already negative balance of the infant is made greater. Presumably this effect is produced by the oxalate content. Spinach has the same effect on the calcium balance, probably for the same reason. Spinach seems to serve little useful purpose in supplying the mineral needs of the body, Popeye to the contrary notwithstanding.

The proprietary cereal food pablum contains 6.8 mg. of iron to the ounce of dry preparation. This is a higher proportion of iron than is found in any of the natural foods. Much of this iron is in the powdered alfalfa content. Balance experiments show that the iron of pablum is well utilized. The utilization is better than that with egg yolk and the same as that with ferric ammonium citrate.

It has long been recognized that iron ammonium citrate is well utilized. This material is not a definite crystalline substance, but varies somewhat in its iron content. One cubic centimeter of a 1 per cent solution contains 1.5 to 2 mg. of iron. In order to meet the iron requirement of the infant up to one year of age,

5 c.c. of a 1 per cent solution is ample. This supplies from 7.5 to 10 mg. of iron. More than this amount is unnecessary and amounts greatly in excess are likely to be definitely harmful. Though babies need more iron than most of them get, the overzealous administration of iron will do more harm than good.

Vitamin D

Vitamin D as it occurs in nature or is produced by irradiation is of two varieties, one of animal origin related to cholesterol and the other of vegetable origin related to ergosterol. On a rat unit basis these two varieties have markedly unequal values for the chick and to a lesser degree for the human infant. The evidence may be interpreted to indicate that approximately 1.5 times as many rat units of vegetable source vitamin D are required as of animal source vitamin D to produce the same effects in the human.

The smallest amount of vitamin D recommended to the public as being adequate is the amount found in irradiated milk, which contains 135 U. S. P. units to the quart. This amount of vitamin D will prevent and ultimately cure rickets in most instances. It has been found also that cod liver oil concentrate dispersed in milk and cod liver oil separately have the same effects as irradiated milk when administered on an equal rat unit basis.

Rickets prevention has had almost universal acceptance as a criterion of adequacy of vitamin D. If this is an acceptable criterion, 60 to 135 units of animal source vitamin D constitutes an adequate amount, instead of the 1,000 units or more in the recommended dose of 3 teaspoonfuls of cod liver oil. The discrepancy between these two recommendations is more than 600 per cent.

Evidence has been produced to show that rickets prevention is not a criterion of sufficient vitamin D. Babies receiving irradiated milk or its equivalent do not grow as well as those receiving a larger amount of vitamin D. Balance experiments show significantly smaller retentions of calcium and phosphorus with irradiated milk than when the amount of vitamin D in 1 teaspoonful of cod liver oil is administered. If babies receiving irradiated milk have inferior growth and inadequate calcium retentions, this amount of vitamin D cannot be accepted as satisfactory.

The minimum amount of vitamin D which will permit satisfactory growth and calcium retentions has not been determined, but it has been shown that the amount in 1 teaspoonful of cod liver oil is ample and perhaps in excess of the minimum requirement. It is indicated also that amounts of cod liver oil greater than 1 teaspoonful will cause no further increase in growth or in calcium retention. Apparently the maximum beneficial effect is obtained with a 1 teaspoonful daily dose.

Vitamin A

The general impression has obtained that vitamin A deficiency is infrequent in our general population. This opinion has been based on the relative infrequency of xerophthalmia and of night blindness. Apparently xerophthalmia depends on an extreme deficiency, and it is not surprising that this condition is uncommon. Because of the necessity for a marked deficiency in order to produce xerophthalmia, this condition could not be used as a criterion for lesser but significant degrees of vitamin A deficiency. Similarly, night blindness of sufficient degree to be a cause of complaint cannot be a good criterion. Conclusions based on questionnaire surveys concerning the frequency of night blindness must take into consideration the fact that routine ophthalmologic examinations do not detect night blindness. It is diagnosed usually only after complaint is made and special tests applied. It seems probable that significant degrees of night blindness of which the subject is aware are more common than is usually assumed. It is certain that moderate degrees of night blindness of which the subject may be unaware are exceedingly common.

When a special test for dark adaptation is applied, departures from the normal are found with considerable frequency. It is easily demonstrated that at least in the great majority of instances these abnormal results are dependent on vitamin A deficiency; when vitamin A is administered, the subjects develop normal dark adaptation. The great frequency with which vitamin A deficiency is found by this procedure would seem to demand attention. If anything like half of the children of this country are ingesting diets deficient in this respect, some kind of educational propaganda is indicated. It has been determined that a good diet containing ample vitamin A can easily be selected from common readily available foods. When such a diet is used, apparently vitamin A concentrates are not necessary. This fact being recognized, what should be the status of vitamin A concentrates? Should they be recommended for routine use or should their use be discouraged? Should vitamin A additions to foods be permitted?

Educational propaganda directed by nutritionists and physicians to the mass of people at large has had and for a long time may be expected to have only a very limited effect. Propaganda sufficiently extensive to be effective is economically impracticable, and to a considerable extent an urgent incentive is lacking. If we await optimistically the time when all of the people will select good diets because of this type of instruction, many will continue to have dietary deficiencies indefinitely.

On the other hand, if we accept and encourage the commercial exploitation of this need, a potent incentive with economic backing and considerable initiative immediately comes into the picture. Results will be more far-reaching and will be attained more quickly. If people persist in selecting foods containing little or no vitamin A, what possible harm can come from additions of this substance to certain of the most common foods selected for this purpose because of their appropriateness as a vehicle for vitamin A and because of their widespread use?

Observations on the Anti-Infective Action of Vitamin A and on Moderate Deficiency of Vitamin C

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Within the past few years, exact knowledge of the chemical and physical properties of vitamins A, B_1, C, and D has accumulated with breathless speed. Methods for quantitative chemical estimation of carotene, the precursor of vitamin A, for vitamin A and for vitamin C are now available, methods which surpass in delicacy, exactness, and speed the biologic methods. For these reasons, workers sometimes ignore the fact that the chemical and physical methods are specific for the substances in question only when certain criteria are met. If not, conclusions based upon the use of the newer technic will be fallacious. Under properly controlled conditions, however, clinical results otherwise unattainable must result. With the pure vitamins now available, we shall be able eventually to settle with certainty questions of specificity; to determine the actual requirements of these vitamins under various conditions of age, sex, and disease; to discover states of "subclinical" deficiency; and to ascertain the upper limits of safe dosage. Moreover, with pure vitamins, it is possible to avoid the untoward effects which may result from substances which accompany the vitamins in nature.

Our own work has been concerned with the analysis of fluids and tissues of the body for carotene, xanthophyll, vitamin A, and vitamin C. Two questions will be considered: (1) the anti-infective action of vitamin A, and (2) the application of the newer methods to the study of deficiency of vitamin C.

The Anti-Infective Action of Vitamin A

McCollum in 1917 first showed that rats with xerophthalmia were liable to spontaneous infections. This work has been confirmed and extended by many other workers. It has been shown that the spontaneous infections of the respiratory tract are

associated with the metaplasia of the respiratory epithelium characteristic of severe deficiency of vitamin A. The lowering of resistance to experimental infection with the paratyphoid group of organisms in rats may be due in part to metaplasia of epithelium; but, since the barriers of the liver, spleen, and bone marrow failed to prevent bacteremia in the feeding experiments of Lassen, it is evident that some factor other than epithelial metaplasia must be involved. In these experiments the infections were induced after the deficiency had fully developed. Bradford and Boynton, and later McClung and Winters, showed that rats receiving diets deficient in vitamin A became susceptible to infection before loss of weight or any other sign of deficiency developed. This suggests that mild forms of vitamin A deficiency may be a cause of susceptibility to infection. This suggestion receives support from the studies of Webster and Pritchett, who showed that mice raised for generations on a diet hitherto considered adequate were less resistant to inoculation with mouse-typhoid bacilli than were other mice whose diet was supplemented by the addition of cod liver oil or butter. Topley, Greenwood, and Wilson were apparently unable to confirm this work, but in their experiments, the deficient diets were not begun until relatively late in the lives of the mice. In all the work so far mentioned, no analyses were made of the tissues for vitamin A. Some observations of McCoy and McCoord may serve to reconcile the different conclusions of the authors mentioned. In their work, rats of varying age were depleted of vitamin A, as shown by a negative Price-Carr test for vitamin A, and then infected with trichinosis. The young rats were invariably more susceptible than the controls which received supplements of halibut liver oil. The older rats—even though their livers were devoid of vitamin A—were only slightly more susceptible than the controls. More work must be done, using other infecting organisms, various portals of entry, and other hosts. The study of the effect of a deficiency in fetal life or in early infancy, followed by normal diet, would also be of great clinical significance. The experimental work may be summarized by the statements: Frank deficiency of vitamin A in most animals leads to increased susceptibility to spontaneous and to artificial infections. There is no evidence that animals with adequate stores of vitamin A may be rendered more resistant to infection by administering carotene or vitamin A, although there is some evidence that some of the standard diets in use may be so improved.

With this brief discussion of experimental results, we may now consider the evidence for the anti-infective action of vitamin A in man. Bloch in 1928 reported his very extensive observations of xerophthalmia in Denmark and called attention to the frequency of severe infection in his 109 patients. Later he stated his belief that the liability to infection persisted even after cure of xerophthalmia. A liability to infection in xerophthalmia is, however, not evident in the reports of Spense or of Blackfan and Wolbach. Efforts to lessen the incidence and severity of infections in infants without xerophthalmia by the administration of cod liver oil, concentrates of vitamin A, or carotene have on the whole been unsuccessful. Erben reports success; Barenberg and Lewis, and Hess, Lewis and Barenberg report complete failure. Helen McKay finds no increase in resistance to respiratory infections but reports a decrease in infections of the skin. We have noticed in the reports of the work of Hess and his colleagues that only 7 per cent of the infants were under the age of six months and that the diet in very early infancy was not described. Therefore, we have analyzed in our own cases the feeding histories from the age of two months. We find that the addition of cod liver oil to the diet by the age of two months confers no increase of resistance to infection during the first six months of life but that the addition of cod liver oil by the age of two months and the inclusion of vegetables after the age of five months appears to confer considerable resistance between the ages of six and twenty-four months. This effect disappears in large part after the age of two years. The criticism that the control cases may not be comparable with those receiving additions of vitamin A is difficult to meet, for these

cases are largely children of families who failed to follow all kinds of advice. The results, however, suggest that the infant in early life may require very much larger amounts of vitamin A than in later life. Our own work confirms the findings of several other workers that the liver at birth, especially in the case of premature infants, contains very little vitamin A and that colostrum is exceptionally rich in carotene and in vitamin A. We are at present studying the vitamin A requirements of the fetus. The blood of the umbilical vein always contains more carotene than does that of the umbilical artery, whereas the average concentrations of vitamin A in vein and artery are equal. A conservative, if not very accurate, estimate shows that at the time of birth, the fetus may be receiving 1000 international units of vitamin A as carotene per kilogram of weight each day. We are planning to study the effects of early administration of vitamin A upon subsequent tendency to infection in a carefully controlled series of cases.

The influence of administering vitamin A to older children and adults upon resistance to infection has been the subject of many conflicting reports. Mellanby and his coworkers in 1931 claimed that a preparation of vitamins A and D would lessen the incidence of postpartum fever and applied to vitamin A the unfortunate adjective "anti-infective." The term "anti-infective vitamin" has served to stimulate the publication of much uncritical work. Holmes, Pigott, Sawyer, and Comstock administered one tablespoonful of cod liver oil a day to a volunteer group of industrial workers. The incident of common colds and the loss of time from work was less than in a group of "controls" who refused to take cod liver oil. Ellison administered a concentrate containing vitamins A and D in 600 alternate cases of measles. Although the incidence of pneumonia and of otitis media was the same in both groups, the mortality was 3.7 per cent in the group receiving the vitamins and 8.7 per cent in the other. The fact that the two groups occupied separate wards renders the evidence less convincing. Recently several other authors have claimed that the administration of carotene lessened the incidence and severity of respiratory infections.

Equally impressive evidence has been recorded that the administration of vitamin A during an infection does not lessen its severity. Sutliff, Place, and Segod administered 400,000 U. S. P. units of vitamin A per day to 509 children with scarlet fever. The incidence of otitis media was 9.4 per cent. The expected incidence was 11.3 per cent. Alternate cases were not treated.

We have made a similar study, using carotene in scarlet fever, with no beneficial results. Studies of the blood showed that the carotene had been absorbed, although the level of blood carotene was less than that which was produced by the same dose in convalescent children.

For several years we have administered carotene in children living in foster homes. An effort has been made to keep the experimental and control groups as nearly alike as possible. We have been unable to observe any lessening of the incidence of infection or any decrease in its severity in the treated children.

Two chief criticisms can be directed against the clinical reports: (1) It is difficult to be certain that the experimental and the control groups are comparable; and (2) criteria have not been furnished that a deficiency of vitamin A existed in the subjects. From a study of carotinoid pigments of the blood in a large group of children, together with clinical histories of susceptibility to colds, we have concluded that not more than 5 or 10 per cent of the children *might* have been benefited by the administration of carotene. It is obvious that if subjects for the administration of carotene are selected at random, any beneficial effects may not appear on statistical analysis. We need an extensive experiment in which children with habitually low blood carotene are selected for a controlled test. Analysis of the liver, which is the great storehouse of vitamin A, often shows a marked decrease in persons who have died of severe infection. This decrease in vitamin A is not sufficient evidence that these persons

had suffered from a deficiency of vitamin A before the infection. We have found that the stores of vitamin A in the livers of rats are depleted by infection and that the degree of depletion depends upon the severity and the duration of the infection.

It may be concluded that the administration of carotene or of vitamin A cannot be expected to increase resistance to infection in older persons who are not suffering from deficiency of vitamin A. Sufficient studies have not been reported of the anti-infective value of vitamin A in persons who actually are deficient. On the other hand, there is evidence that the young and rapidly growing infant may require abundant vitamin A in order to develop resistance to infection in early life. The actual requirements of vitamin A for this purpose are not known.

Test for Deficiency of Vitamin C

In clinical conditions supposed to be due to deficiency of vitamin C, four diagnostic tests have been proposed:

1. *The "Therapeutic Test."*—The condition must be relieved by the administration of vitamin C. The therapeutic test may be carried out with pure cevitamic acid. A number of reports have appeared on the cure of scurvy and the relief of prescorbutic symptoms by this method. Some years ago, Theobald Smith observed that guinea pigs during the winter were subject to pneumonia, which tendency disappeared as soon as fresh fodder was available. These experiments have been extended by von Euler, who has been able to show that fresh vegetables and fruits contain the anti-infective agent even after the vitamin C in them has been destroyed. These experiments are mentioned in order to show that relief of symptoms with fruit juices may not be proof that these symptoms are due to deficiency of vitamin C.

2. *The Capillary Resistance.*—Göthlin and his coworkers, using a standardized technic for the Leeds-Rumpel test, report decreased capillary resistance in persons consuming a diet low in vitamin C. Dalldorf, using measured negative pressure, reaches the same conclusion. Both investigators find that the administration of vitamin C increased capillary resistance. The reports of Greene and of Toverud fail to confirm the claims of these authors. Abt, Farmer, and Epstein find no relationship between the capillary resistance and the level of reduced cevitamic acid in the plasma. Hawley, Stephens, and Anderson, using a modification of the negative pressure method, observed no increase in capillary resistance in subjects after receiving large amounts of orange juice or of cebione (Merck). In these studies the daily output of cevitamic acid in the urine was measured. Hawley has observed one case of scurvy in which a marked and prompt increase in capillary resistance followed the oral administration of cebione and another, in which the capillary resistance was normal. She has also observed one case of thrombopenic purpura in which there was a close correlation of capillary resistance with the intake of vitamin C over a period of many months. In several other cases of purpura no such correlation was observed. Her observations seem to indicate that the discordant reports in the literature are not due to differences in technic or interpretation, but depend upon factors not understood. It is obvious that the tests of capillary resistance are not reliable indicators of vitamin C deficiency at the present time.

3. *Chemical Analysis of Urine for Vitamin C.*—Under proper conditions, titration of urine with the indicator 2:6-dichlorphenolindophenol is an accurate measure of its content of vitamin C. The iodine titration, reliable for certain fruits and vegetables, gives high results with urine, mainly owing to the presence of sulphur compounds. Using the dye method, Harris and his colleagues have shown that the urinary output of vitamin C is an accurate measure of the intake of vitamin C. The claim of Beszonoff that infants under four months of age are able to synthesize vitamin C appears to be unfounded. Abt and his colleagues believe that the excre-

tion of vitamin C, observed by Beszonoff, is wholly explained by the slow elimination of the stored vitamin. Hawley is at present engaged in a study of the vitamin C content of human colostrum and milk. She has shown that an increase follows within an hour after the ingestion of orange juice. She is also observing the output of cevitamic acid in the urine of infants on various analyzed diets and finding a close correlation between intake and output. She finds no evidence that the young infant is able to synthesize its own vitamin C. We have observed that patients receiving diets for gastric ulcer are invariably undersaturated with vitamin C. In nephritis the output of vitamin C is likely to be low. This is in part due to the rapid disappearance of vitamin C in the urine itself. The acid-base balance of this diet also affects the output of vitamin C when the intake is constant. Hawley and her coworkers have conducted an extensive experiment showing clearly that the measured output of vitamin C is reduced when the urine is alkaline. They have shown that the loss of vitamin, due to its destruction of oxidation in a medium as alkaline as the urine in question, does not wholly explain their results. An experiment involving the analysis of tissues of guinea pigs on various diets is in progress in the attempt to account for the findings. It is apparent that analysis of urine is an important and reliable method of investigation.

4. *Analysis of Blood and Tissues.*—The reports of Abt and his colleagues indicate that analysis of blood may become a satisfactory method for diagnosis of scurvy and prescorbutic conditions. Our own observations, few in number, fully confirm this opinion. Unpublished results of Clayton show that the tonsils contain abundant cevitamic acid and that the concentration depends upon the previous diet. She has observed a decrease in chronic infections but has not been able to show exceptionally low values in rheumatic fever.

Conclusions

The newer chemical and physical methods for quantitative estimation of vitamins A and C afford useful tools for the investigation of clinical problems. They will prove most fruitful as a supplement to accurate clinical observation.

GENERAL DISCUSSION

DR. JOHN ZAHORSKY (St. Louis).—I desire to bring up the question of overgrowth in infants. The high protein content of modern milk mixtures fortified by concentrated vitamin has a distinct tendency to product an overgrowth. It is very common now to obtain the same growth in the first year which we formerly believed required two years. Moreover, the fontanel is closed in so many of these infants at one year or less. The brain, however, does not quite keep pace with this somatic growth. The question whether this overgrowth during infancy is ultimately advantageous or detrimental to the child requires serious consideration. In animals the growing period to maturity can be shortened by heavy feeding. Are we going to shorten the period of childhood by this superalimentation?

In a study of 50 infants who were overgrown, we find a distinct tendency for the weight to approach the normal after the infant is eighteen months old. This makes it necessary that the child stop growing and, I believe, is the prime impulse in the nervous anorexia so common at this period. The administration of vitamins A and C regardless of the rate of growth seems entirely irrational. The child stops eating but he has to swallow viosterol. I am discouraging the routine use of the concentrated vitamin during the summer months and after the third year.

CHAIRMAN MARRIOTT.—Dr. Zahorsky is to be congratulated on the excellent nutritional results he obtained. The good nutritional results with generous feedings last to adult life.

The observations of Gray on boys in a private school showed that children of the better classes, well fed from the age of infancy, averaged distinctly larger than accepted normal standards. We know further that children today with better methods of nutrition are decidedly taller and heavier than the children of ten or fifteen years ago.

DR. JEANS.—Mental tests show higher ratings for babies who grow well. For several seasons it has been observed that babies kept on low vitamin D intake for experimental purposes did not do well. I think that 1 dram of cod liver oil is enough even under poor conditions if the food is good.

DR. JAMES A. WHEELER (NEWTON, KAN.).—Dr. Zahorsky stated that he wonders what will happen to the mental side of children by the newer feeding standards. I have been informed by several men who have worked in the child guidance centers that the problem is not strictly confined to the child but is mainly one with the parents. Most of these parents were fed under earlier methods.

DR. JOHN R. VONACHEN (PEORIA, ILL.).—Since Dr. Marriott mentioned the possible relationship between a high protein intake and premature senility, it occurred to me that there might be some connection between this and progeria. I remember the case of progeria because of its unusualness in that this child had taken between two and three quarts of lactic acid milk up to the age of almost three years. I saw her when she was about twelve years of age, not because of the high lactic acid milk intake but for the progeria. This child was so fond of the lactic acid that she preferred it to other milks. I mention this because of its unusual occurrence rather than it had anything to do with the progeria. However, I would like to ask Dr. Marriott if there could be any possible relationship.

CHAIRMAN MARRIOTT.—I doubt if there could be any relationship.

DR. MAURICE L. BLATT (CHICAGO).—What is the advantage of excess weight with monosaccharides?

DR. JEANS.—The large gains reported were in children who were 20 to 30 per cent underweight. Gains can be made better with a high dextrose diet than with fat. The increased gain tended to cease when the child had attained normal weight.

DR. BLATT.—In considering the weight of a child, its chronologic age, its height, whether it was premature or full term, and its build have to be taken into consideration. Children usually resemble their ancestors in stature. It does not seem important that a child be given additional food for no other purpose than to put on weight. In my experience, thin children enjoy quite as good health and are quite as long lived as are fat ones. Lack of weight due to disease is, in my opinion, not well treated by feeding carbohydrate for the purpose of increasing weight. A gain in weight occurring in a child ill with an infection is usually an indication of the child's general improvement.

DR. ARTHUR F. ABT (CHICAGO).—What significance does Dr. Marriott attach to the relationship, stressed by L. F. Meyer of Berlin, between fat and carbohydrate which is a 1 to 2 ratio in breast milk? Meyer contends that the failure of every effort with straight cow's milk has been solely due to its 1:1 ratio. He further believes that fat restricts, while carbohydrate favors, water retention and that for the normal metabolism of the human infant the 1:2 ratio of fat to carbohydrate is necessary.

CHAIRMAN MARRIOTT.—Most infants do somewhat better when the proportion of carbohydrate exceeds that of fat, but that this is not necessarily the case

has been repeatedly demonstrated in the case of diabetic infants and children, in whom excellent nutrition has been maintained on high fat diets containing a minimum of carbohydrate.

DR. JAY I. DURAND (SEATTLE, WASH.).—How much milk should a child take?

CHAIRMAN MARRIOTT.—I do not know. It depends upon the child. If one refers to the experiments of Dr. Clara Davis and the experience of children in the tropics, it is recognized that one gets good results with a varied diet.

DR. JEANS.—The criterion may be the calcium intake rather than other food. Milk is the chief source of calcium.

DR. EVON ROSENSTERN (BERLIN, GERMANY).—At one time our children were getting a liter or more of milk. They were fat and had poor resistance. Lately we have given less milk, one-half liter, and more vegetables. The state of health on this schedule is better. The height of the population in Germany during the last fifty years has increased about 5 cm. In recent years the height of children was lessened. There were various theories as to the cause of that. It was thought to be due to lack of food after the war or due to rickets that many children developed before and after the war. We studied the growth of breast-fed and artificially fed babies and noted that the calcification centers developed earlier with artificial feeding.

DR. ZAHORSKY.—Does the incidence of rickets in infancy and early childhood have a tendency to produce shorter adults? I have a distinct impression that moderate rickets without deformity has no effect on the final height of the person. Or is this due to the fact that rickets occur generally in the infant who has a natural tendency to be tall?

CHAIRMAN MARRIOTT.—Many individuals who have had severe rickets during infancy and early childhood remain permanently dwarfed.

DR. JEANS.—I think that growth will be compensated later if the rickets was not too severe. I am not sure that the improvement in children referred to by Dr. Rosenstern is due to less milk or to other food given.

DR. B. FEINBERG (PROVIDENCE, R. I.).—I wonder whether Dr. Marriott has had any experience with small doses of thyroid in premature infants?

CHAIRMAN MARRIOTT.—We have not had any experience in the use of thyroid in normal premature infants.

DR. MARTHA M. ELIOT (NEW HAVEN, CONN.).—1. Dr. Jeans has indicated the efficacy of vitamin D in relation to growth. Does he think 1 teaspoon of cod liver oil will provide a sufficient margin of safety?

2. If 400 units are believed to be necessary for optimum calcium retention, should additional vitamin D be given to infants and children besides that contained in irradiated milk?

3. What is the easiest way to give the required amount of iron to infants? Is ferric ammonium citrate the best form? Should it be recommended routinely in well baby conferences, or should it be considered as a drug to be prescribed only by physicians? Would it be your opinion that the Children's Bureau should recommend the prophylactic use of iron in their publications?

DR. JEANS.—1. From our data it is indicated that when 1 teaspoonful of cod liver oil is ingested, the retention of calcium and phosphorus approaches closely or equals the maximum to be obtained. Presumably nothing is to be accomplished by larger amounts of vitamin D, and 1 teaspoonful of cod liver oil provides a sufficient margin of safety.

2. It is my opinion that the amount of vitamin D in irradiated milk as now produced is insufficient for the best nutrition of the infant and that additional vitamin D should be given. The requirement of the child past infancy is not known. It is the general belief that the child requires less than the infant, but the evidence for any belief is meager.

3. Much thought must be given to the infant's diet in order that sufficient iron may be obtained from food sources alone. It would seem a measure of safety to add one of the iron salts. Iron in the amount we have discussed could scarcely be considered harmful. Probably iron and ammonium citrate should not be stated as the best preparation, but it has seemed entirely satisfactory. The use of iron in the manner discussed should be considered from the nutritional point of view and could be recommended appropriately by anyone competent to give nutritional advice. I know of no reason why the Children's Bureau should not recommend the prophylactic use of iron if the director so desires.

DR. FRANK H. DOUGLASS (SEATTLE, WASH.).—When can we stop giving cod liver oil? When does rickets stop?

DR. JEANS.—It is our own preference to continue the use of cod liver oil throughout the period of childhood. The additional amount of both vitamins A and D may be considered advantageous.

Though rickets of the type caused by vitamin D deficiency is uncommon after two years of age, increased, and presumably more desirable calcium retentions are obtained, at least during the winter months, when cod liver oil or some equivalent is ingested. Increased calcium retentions appear to have a direct relationship to the prevention of tooth decay, which is so prevalent in childhood.

DR. FEINBERG.—1. What are the relative merits of vitamin D present in certified milk from cows on a ration of irradiated yeast and milk irradiated directly?

2. Do you feel that additional vitamin D in form of cod liver oil is necessary?

3. Do vitamin D concentrates have the same effect as vitamin D in the form of cod liver oil?

4. The iron question is very interesting. Do you feel that the comparatively small dose of iron and copper, such as is present in some of the proprietary sugars, as Abbott's cofron-maltose, is sufficient to prevent a negative iron balance during the first few months of life?

5. Are large doses of iron given to the mother during the latter months of pregnancy effective in preventing nutritional anemia in the infant?

DR. JEANS.—1. Yeast milk is usually produced with 430 U. S. P. units of vitamin D to the quart and irradiated milk, with 135 units to the quart. Some have considered that the relative value of these two milks is directly proportionate to the vitamin D unitage. Even if yeast milk proves to be less potent than irradiated milk, on a unit-for-unit basis, the difference is not great and a marked advantage still exists in favor of yeast milk because of the greater vitamin D content.

2. It is my opinion that the amount of vitamin D in irradiated milk is not sufficient to meet the needs of the infant and consequently additional vitamin D from some source is indicated. The amount of vitamin D in yeast milk probably is sufficient.

3. For all practical purposes, it may be stated that vitamin D concentrates have the same effect as the vitamin D of cod liver oil. When the dose is reduced to minimum levels the probability that vitamin D of vegetable source is less potent than that of animal source must be considered. It is generally agreed that at the minimum effective level more units as viosterol are required than as cod liver oil. With customary dosages, however, this difference need not be considered because both materials are commonly administered above the level which produces the maximum physiologic effect. In considering a choice among vitamin D preparations, one should not lose sight of a possible need for vitamin A.

4. I do not know the iron content of cofron-maltose, but if it supplies 10 to 25 mg. of iron a day, as I believe it does, this amount of iron is ample not only to prevent a negative balance but also to allow a good retention after two months of age. A negative balance during the period of hemoglobin destruction in the first two months does not have the same significance as it does later.

5. The store of iron in the liver at birth depends appreciably upon the iron intake of the mother. When the mother's intake has been low the store of the infant may be negligible and also the amount of hemoglobin less than normal. On the other hand, the liver storage is not great under the most favorable conditions. The later storage from hemoglobin destruction is always greater and therefore more important than the amount present at birth. It has been found that ingestion of 20 mg. of iron daily by the mother during pregnancy permits ample storage for her and the infant.

DR. EARL W. MAY (DETROIT).—1. Dr. Jeans, have you used irradiated milk higher than 135 units?

2. We have been using irradiated milk with 150 units and have found it most effective in the prevention of rickets and the maintenance of normal growth in the normal full-term infant.

DR. JEANS.—1. We have not. Such a milk has not been available to us.

2. The difference between 135 and 150 units to the quart is not great, and a marked difference in results would not be expected.

What is normal growth? The growth curves of Stuart published in 1933 and of Kornfeld published in 1929 show greater rates of growth than those published by Baldwin in 1921. This indicates that nutritional conditions are improving. Even the more recent studies of Kornfeld and Stuart have included individuals who had been receiving poor nutritional care, as well as those whose care had been good. Perhaps we should think of the ideal growth curve only in terms of good nutritional and hygienic care. In such case the rate of growth will be greater than that recorded in the Stuart and Kornfeld studies. Thus, good or optimal growth represents more rapid growth than the published averages now available.

DR. BLATT.—Three children in my practice receiving vitamin D milk have had gastrointestinal disturbances associated with diarrhea. Their diarrhea ceased on ordinary pasteurized milk, but they did not progress as satisfactorily as do most of the children whom we feed without the use of this irradiated product. They were more irritable, muscle and bone development was not as satisfactory, nor did they have the regularity of weight curve increase which I am accustomed to see in my practice.

DR. JEANS.—We have had no experience with irradiated milk causing diarrhea.

DR. ROGER MOORE (ST. JOSEPH, MO.).—Dr. Jeans stated that 1 dram of cod liver oil was sufficient. Will there be a deficiency of vitamin A in such a dose?

DR. JEANS.—I do not know the infant's requirement for vitamin A, but there has been no obvious evidence of vitamin A deficiency with such a dose.

DR. F. W. SCHLUTZ (CHICAGO).—What is the comparative prevalence of night blindness in urban and rural children, and what relation has this prevalence to the diet?

DR. JEANS.—In our survey of Iowa children subnormal dark adaptation was found in 26 per cent of the strictly rural group, 53 per cent of the village group, and in from 56 to 79 per cent of the urban group, the variation in the last group depending upon the economic level. It may readily be assumed that the prevalence found has a direct relationship to the type of diet, inasmuch as improvement in the diet nearly always corrects the difficulty.

DR. BLATT.—1. Is night blindness higher in cases with infection?
2. Does carotene drop in the winter?

DR. CLAUSEN.—1. Cases with infection have a low carotene perhaps due partly to lack of appetite.
2. Carotene is low in the winter and rises in March and April to a plateau with a slight rise and then a fall to January.

DR. DURAND.—1. How old were the children with night blindness?
2. Did any children with night blindness get cod liver oil?
3. Did you find more infection in the group with night blindness?

DR. JEANS.—1. The ages of the children with night blindness ranged from six to fourteen years. Children at other ages were not examined.
2. None of the children with night blindness were receiving cod liver oil.
3. No observations were made concerning the incidence of infections in children with night blindness.

DR. WHEELER.—I should like to ask Dr. Jeans if after further observation on vitamin A experimentation he is still of the opinion that mineral oil destroyed the absorption of vitamin A in the intestine.

DR. JEANS.—Mineral oil has a very decided effect in depleting the body of vitamin A, particularly when the intake of vitamin A is low or borderline as compared to the probable requirement.

DR. WHEELER.—Can the photometer test be used as a standard for determining vitamin A deficiency?

DR. JEANS.—The photometer is used as a means for detecting abnormal dark adaptation. Poor adaptation is caused by vitamin A deficiency in most, but not in all, instances. With these few exceptions, which are recognizable by ophthalmologic examination, the photometric test can be used as a standard for determining vitamin A deficiency. A new photometer is now available, which permits greater precision and ease of use than the one formerly employed.

DR. DOUGLASS.—What is carotene besides vitamin A and pigment? I ask this question because of the favorable results we have seen in cases of albinism in which the administration of carotene in oil has increased the color of the retina. Is it due to pigment or vitamin A?

DR. CLAUSEN.—The several isomeric carotenes are produced only by plants. They are hydrocarbons with the formula $C_{40}H_{56}$. One molecule of beta-carotene is transformed in the animal into two molecules of vitamin A, an alcohol with the formula $C_{20}H_{29}OH$. It is not yet known whether carotene as such performs any special function in the animal body aside from its function as precursor of vitamin A. When large quantities of carotene are ingested, especially when the carotene is not destroyed, the skin may become pigmented; it is possible that the retina may share in this pigmentation and that the process would be more apparent in an albino than in a normal person.

DR. MARGARET NICHOLSON (WASHINGTON, D. C.).—Is cod liver oil better than viosterol? Does the absence of vitamin A in viosterol make a difference?

DR. CLAUSEN.—Comparative studies by Hess and Lewis indicated that infants receiving cod liver oil had about as frequent and severe infections as infants receiving viosterol and that large additions of vitamin A to the diet in the form of carotene or halibut liver oil conferred no increase of resistance to infection. They concluded that the milk of the diet furnished enough vitamin A. However, most

of the infants studied by them were over six months of age. We have, therefore, compared the incidence and severity of infection in infants who received cod liver oil at least from the third month with the incidence and severity of infection in infants who did not, and we have found an apparent considerable increase of resistance during the latter half of the first year of life. Our work is open to the criticism that other factors than lack of vitamin A may play rôles in the control group of infants. I feel that your question can be answered only when we know more about the requirements for vitamin A in the early months of life.

DR. MAURICE J. LONSWAY (ST. LOUIS).—I should like to ask Dr. Jeans if he has seen any bad effects with larger doses of iron. We give larger doses than he advises to premature infants, and it is our impression that they do quite well with no observable ill effects.

DR. JEANS.—Doses in excess of 25 mg. a day probably will do no good. We have observed no actual harm from larger amounts, but we have not studied the metabolic effects in detail.

DR. BLATT.—Do premature infants retain iron?

DR. JEANS.—They break down hemoglobin during the first two months and do not need iron during this period. The prematurely born infants we have studied have retained ingested iron after two months of age.

DR. ABT.—1. Do you still believe in Bunge's conception of the iron reservoir in the liver at birth?

2. Were the children who had a negative iron balance on breast milk or cow's milk?

3. Was the specific dynamic action of protein taken into account in the values you gave for creatinine excretion?

4. Are there any references in the literature as to the absorption of cod liver oil? It is not an uncommon experience, in calling at the homes of my patients, to have the mother show me the baby's diaper containing the stool and often a distinct separate oily substance which looks and smells like cod liver oil. When we state the optimal dose, must we not then allow for the amount of nonabsorbed oil (if a portion of the oral dose is not absorbed)?

5. Are there any other experiments recorded in the literature besides those which Dr. Jeans mentioned which substantiate the statement that spinach is a demineralizer?

DR. JEANS.—1. Apparently a small store of iron exists normally in the liver at birth. However, this store is relatively unimportant when compared to the amount of iron which becomes available from the destruction of hemoglobin in the early weeks after birth.

2. The infants with a negative iron balance were receiving cow's milk.

3. No, this was not considered. It is probable that this factor relates more closely to creatine than to creatinine excretion.

4. I am not familiar with the literature on this subject. My statements concerning the dose of cod liver oil were based on the usual or average utilization. In my own experience, failure of utilization has been exceptional. In such a case it seems doubtful that increase of the intake will increase the absorption. Some other source of vitamin D would seem indicated.

5. Dr. Schlutz and his coworkers have pointed out the lack of value of spinach as a source of iron for infants (J. PEDIAT. 3: 225, 1933).

DR. H. G. PONCHER, CHICAGO, ILL.
Recorder.

Academy News

The annual meeting of Regions I and II of the American Academy of Pediatrics will be held in Baltimore, Md. The headquarters will be at the Belvedere Hotel, Charles and Chase Streets. The following men are in charge:

Louis C. Schroeder, New York, N. Y., Chairman, Region I; Phillip Van Igen, New York, N. Y., Acting Chairman, Region I; Edward Clay Mitchell, Memphis, Tenn., Chairman, Region II; Baltimore Committee on Arrangements, Fred B. Smith, Chairman, L. Emmett Holt, Jr., C. Loring Joslin, J. H. Mason Knox, Jr., D. C. Wharton Smith.

The following program has been announced:

MONDAY, NOVEMBER 16

9:30 A.M. Hurd Auditorium, Johns Hopkins Hospital.

An Unusual Type of Bone Dystrophy Resembling Paget's Disease, With Presentation of a Case—Dr. Laslo Kajdi.

Presentation of Two Cases of Porphyria—Dr. Harriet G. Guild.

Certain Aspects of Serum Therapy in Meningococcus Meningitis—Dr. Francis F. Schwentker.

A Study of the Rate of Growth and Osseous Development in Hypothyroidism and Dwarfism—Dr. Lawson Wilkins.

Newer Concepts of the Achondroplastic State—Dr. Walter Block.

The Treatment of Gonococcal Vaginitis With Amniotin—Dr. Richard W. TeLinde.

The Cause of Icterus Neonatorum—Dr. Nicholson J. Eastman.

Observations on Hypertension in Childhood, With Particular Reference to the Rheumatic State—Dr. Helen B. Taussig.

Renal Hyperparathyroidism—Dr. Edwards A. Park.

Child Hygiene Program in Maryland—Dr. J. H. Mason Knox and associates.

12:30 NOON. Luncheon and meeting of state chairmen, Belvedere Hotel.

1:00 P.M. Luncheon at Welch Memorial Library.

2:00 P.M. X-ray Changes and Prognosis in Pulmonary Tuberculosis in Young Children—Dr. Miriam E. Brailey.

Experiences With Suipestifer Infection in Childhood—Dr. John A. Washington.

A Study of Chronic Nephritis in Childhood—Dr. Alexander J. Schaffer.

Experiences With Esophageal Injury Following the Ingestion of Corrosives—Dr. R. Campbell Goodwin.

The Surgical Treatment of Bronchiectasis—Dr. William F. Rienhoff, Jr.

The Possibilities of Active Immunization Against the Pneumococcus in Different Age Groups—Dr. Lloyd D. Felton.

Congenital Reading Disability—Dr. Leo Kanner and Dr. Angus L. McLean.

The Study of the Anemic Child—Dr. Hugh W. Josephs.

A Study of the Causes of Xanthochromia in Spinal Fluid—Dr. Frank H. Robinson, Jr.

Essential Familial Lipemia—Dr. Francis X. Aylward and Dr. L. Emmett Holt, Jr.

7:00 P.M. Annual banquet at Belvedere Hotel.

TUESDAY, NOVEMBER 17

9:30 A.M. Wilson Memorial Amphitheatre, University of Maryland Hospital.

Intracranial Hemorrhage of the Newborn: With Presentation of Cases Previously Treated—Dr. C. Loring Joslin.

Clinical-Pathological Discussion of Birth Hemorrhage—Dr. Charles Bagley.

Hypertension Associated With Embryonal Adenosarcoma: A Report of Three Cases—Dr. J. Edmund Bradley.

A Study on the Feeding of Whole Milk, Acidified Milk, and Gelatinized Milk, With Especial Reference to Calcium and Phosphorus Absorption—Dr. I. Meranski.

Banana Therapy in Diarrheal Diseases—Dr. Thomas A. Christensen.

Acute Empyema in Children—Dr. Cyrus Horine.

Xanthomatosis of Bone—Dr. Allen Voshell.

The Vitamin B Complex: An Experimental and Clinical Study With Special Reference to Growth and Constipation—Dr. A. H. Finkelstein.

Complications of Accessory Nasal Infections in Children—Dr. Edward A. Looper.

Presentation of a Case of Spontaneous Pneumothorax—Dr. Edgar Friedenwald and Dr. Bowers Mansdorfer.

Persistent Pyuria, Due to Congenital Urethral Malformation: A Case Report—Dr. Fred B. Smith and Dr. A. J. Gillis.

2:00 P.M. Regional business meetings to be held separately. There are a number of important questions to be decided. This is probably the most important session of the regional meeting. It is earnestly requested that all members in attendance at the general meeting be present.

The annual meeting of Region III will be held in Cincinnati, Ohio, Nov. 20 and 21, 1936, with headquarters at the Netherland Plaza Hotel. In addition to the scientific program given in three sessions, there will be a dinner on Friday evening at the Netherland Plaza Hotel with an interesting program.

The following scientific program has been announced:

FRIDAY, NOVEMBER 20

10:00 A.M. to 12:00 NOON. Netherland Plaza.

Use of Supravital Technic in Studying Children's Diseases—C. R. Rittershofer.

Significance of Albumin-Globulin Ratio in Nephrosis—H. W. Robinson.

Relation of Hemoglobin Content and Red Cell Size to Age and Nutritive Condition—George M. Guest.

Hypoglycemia Versus Hyperinsulinism—Stanley Dorst.

Stimulation With Histamine on Gastric Flow—Leon Schiff.

On Significance of Repeated Tuberculin Tests—Waldo E. Nelson.

Alkalosis—Glenn E. Cullen.

2:00 P.M. to 4:45 P.M.

Diagnosis and Treatment of Irritative Symptoms of the Central Nervous System of the Newborn—Harold F. Downing.

The Premature Department of the Cincinnati General Hospital—Edward A. Wagner.

Behavior Problems of Children—E. A. North.

Possible Relation of Various Types of *B. Coli* to Enteritis—Merlin I. Cooper.

Benign Lymphocytic Meningitis (Aseptic Meningitis)—Frank E. Stevenson, Robert A. Lyon, and Clyde Dummer.

Epidemic of Pleurodynia in Children in the Summer of 1935—Robert McDonald, Barbara Hewell, and Merlin L. Cooper.

Pellagra in Children and Present Status of Pellagra—Tom D. Spies.

Vitamin D Content of Serum—Josef Warkany.

Relation of Liver to Ketosis—I. Arthur Mirsky.

SATURDAY, NOVEMBER 21

10:00 A.M. to 12:00 NOON. Children's Hospital Research Foundation Auditorium.

A Case of Congenital Heart Disease With Familial History—Robert H. Kotte.

Method of Blood Matching for Transfusions—Paul Hoxworth.

Report of an Unusual Condition Involving the Bones in a Ten-Year-Old Boy—Leo S. Friedman.

A Case of Unilateral Communicating Hydrocephalus Improved by Ureteral Dural Anastomosis—J. Victor Greenebaum and Henry Freiberg.

Connection Between Pyarthrosis of the Hip Joint and Pelvic Abscesses—Albert H. Freiberg and Joseph A. Freiberg.

The Diagnostic Use of Specific Antiserum in Intradermal Tests—Lee Foshay.

Relation of Endocrine Disorder to Hereditary Deviations—Josef Warkany and A. Graeme Mitchell.

The fifth annual meeting of Region IV was held on Oct. 22 to 24, 1936, in San Francisco, Calif. An interesting scientific program was presented, and a business meeting for the Region was held. Dr. Karl F. Meyer was invited to speak on "Neurotropic Viruses and the Diseases Caused by Them."

Dr. Dorman E. Lichty, of Ann Arbor, Mich., has just been elected a member of the Academy.

Dr. N. N. Allen, of Houston, Texas, died on Sept. 22, 1936. Dr. Allen was a fellow of the Academy and was one of the pioneers in pediatrics in Texas. He was very much loved in Houston and was a great friend of the young men.

Dr. Charles Schott, of Chicago, Ill., died Oct. 1, 1936. He was a fellow of the Academy of Pediatrics.

Dr. Robert K. Rewalt, of Williamsport, Pa., a well-known pediatrician of that state, died suddenly July 27, 1936. Dr. Rewalt was a fellow of the Academy of Pediatrics.

The following appointments have been made by the Executive Board:

Dr. A. Graeme Mitchell, of Cincinnati, to the chairmanship of the Committee on Nursing Education. Dr. Lucas resigned the chairmanship but remains on the committee.

To the Committee on Medical Education, Subcommittee on Postgraduate Education: Dr. George M. Lyon, Huntington, W. Va., chairman; Dr. Horton Casparis, Nashville, Tenn.; and Dr. Hugh L. Dwyer, Kansas City, Mo.

The Michigan Section of the American Academy of Pediatrics held its fall meeting on Sept. 24, 1936. The members attended the meetings of the Pediatric Section of the Michigan State Medical Society on September 24 and 25.

Preceding the meeting a dinner was held at the Hotel Statler in Detroit. Thirty members were present to honor R. Cannon Eley, of Boston, who was in Detroit to speak before the Michigan State Medical Society. Following dinner, reports of the committee appointed to cooperate with the State Health Department on matters pertaining to the Social Security Act and the Committee on Postgraduate Education were read and approved.

The members decided to hold the next meeting in January in conjunction with the meeting of the Detroit Pediatric Society.

Edgar E. Martmer, chairman for Michigan, announced the complete reorganization of the department of pediatrics at Wayne University, Detroit, and the acceptance of the position as head of the department of pediatrics by Thomas B. Cooley, past president of the American Academy of Pediatrics.

News and Notes

A bulletin announces the postponement of the **Fourth International Congress in Pediatrics.** The date is now definitely set for Sept. 27, 28, 29, and 30, 1937. The Congress probably will be followed immediately by the Second International Congress for the Protection of Infancy. Dr. L. Emmett Holt, Jr., Baltimore, is secretary of the American committee.

The **Central New York Pediatric Society** held its fall meeting in Schenectady on October 1. A clinical program was presented at the Ellis Hospital, and after a business meeting at the home of Dr. Frank Van Der Bogert, president of the Society, a dinner was served at the Mohawk Club. Dr. Whitney, of the General Electric Company, addressed the dinner meeting.

Pediatricians from Rochester, Auburn, Watertown, Utica, Schenectady, Albany, Troy, and Syracuse were present.

On September 19 the **Subcommittee on Child Hygiene of the Committee on Public Health and Medical Education, New York State Medical Society,** held a meeting in New York City with Dr. E. S. Godfrey, commissioner, state department of health, several officers of the state Society, and a small group of pediatricians.

The plan of the meeting was to outline a program on child hygiene through the various county societies.

A radio forum entitled "Growth and Development of the Child" will be given under the joint auspices of the **National Congress of Parents and Teachers,** the **American Academy of Pediatrics,** and the National Broadcasting Company.

COMMITTEE

Mrs. B. F. Langworthy, president, National Congress of Parents and Teachers, Chicago; C. A. Aldrich, M.D., Winnetka, Ill., and Henry F. Helmholz, M.D., Rochester, Minnesota, representing the American Academy of Pediatrics; Miss Judith C.

Waller, director of education, central division, National Broadcasting Company, Chicago; Mrs. John Sharpless Fox, Chicago, representing the radio forum committee of the Congress.

1.	Oct. 21, 1936	Introductory: What Is Growth?—Lawrence K. Frank.
2.	Oct. 28, 1936	Prenatal Growth—George L. Streeter.
3.	Nov. 4, 1936	Growth of Infants—Harry Bakwin.
4.	Nov. 11, 1936	Growth of the Adolescent—Horace Gray.
5.	Nov. 18, 1936	Growth of Organs—R. E. Scammon.
6.	Nov. 25, 1936	Our Ancestors—E. A. Hooton.
7.	Dec. 2, 1936	Does Like Beget Like?—Amos H. Hersh.
8.	Dec. 9, 1936	Measurements of Growth—Harold C. Stuart.
9.	Dec. 16, 1936	Individual Variations in Infants and Children—Alfred H. Washburn.
10.	Dec. 23, 1936	Foods and Growth—E. V. McCollum.
11.	Dec. 30, 1936	Chemical Elements and Their Part in Body Growth—S. Z. Levine.
12.	Jan. 6, 1937	Energy and Growth—A. A. Weech.
13.	Jan. 13, 1937	Our Glands—R. G. Hoskins.
14.	Jan. 20, 1937	The Action of Glands on Growth—Oscar Riddle.
15.	Jan. 27, 1937	Effects of Light, Sun, and Other Rays on Growth—Otto Glasser.
16.	Feb. 3, 1937	Heredity or Environment?—E. C. MacDowell.
17.	Feb. 10, 1937	How the Mind Grows in Infancy—Arnold Gesell.
18.	Feb. 17, 1937	How Children's Minds Grow—Walter R. Miles.
19.	Feb. 24, 1937	The Importance of Music for Growing Children—Walter Damrosch.
20.	Mar. 3, 1937	Emotional Development in Children—John E. Anderson.
21.	Mar. 10, 1937	The Connection Between Mind and Body Growth—Bert I. Beverly.
22.	Mar. 17, 1937	Fitting the Course of Study to the Child's Mental Development—Carleton Washburne.
23.	Mar. 24, 1937	Education and Mental Growth—Frank N. Freeman.
24.	Mar. 31, 1937	Athletics, Exercise, and Fatigue in Growing Children—D. B. Dill.
25.	Apr. 7, 1937	Physical Education for Growing Children—C. W. Savage.
26.	Apr. 14, 1937	Disease and the Doctor's Side of Growth—Joseph Brennemann.
27.	Apr. 21, 1937	The Effects of Family Income on a Child's Growth—Martha M. Eliot.
28.	Apr. 28, 1937	The Effect of Child Labor on Growth—Richard A. Bolt.
29.	May 5, 1937	Growth of Children During Wars and Depressions—Carroll E. Palmer.
30.	May 12, 1937	Health Hazards in the Period of Growth—Louis I. Dublin.
31.	May 19, 1937	Old and New Thoughts About Growth—Henry E. Sigerist.

Editor, Norman C. Wetzel, M.D., Babies and Childrens Hospital, Cleveland, Ohio. Music selected and arranged by Leon Machan, pianist, Cleveland Symphony Orchestra.

Dr. R. Langley Porter retired as dean of the School of Medicine, University of California, San Francisco.

Dr. W. McKim Marriott, of St. Louis, was appointed dean of the School of Medicine and professor of experimental research, University of California, San Francisco. Dr. Marriott, who succeeds Dr. Porter, assumed his duties on July 1, 1936.

Dr. Alexis F. Hartmann, of St. Louis, was appointed professor of pediatrics, School of Medicine, Washington University, and chief of staff of the St. Louis Children's Hospital. Dr. Hartmann succeeds Dr. Marriott. Dr. Hartmann assumed his duties on July 1, 1936.

The American Pediatric Society will hold its next annual meeting at University, Virginia on April 29, 30, and May 1, 1937.

The following men have been certified by the **American Board of Pediatrics** since the last report.

Harry S. Altman, New York, N. Y.
Louis Barash, New York, N. Y.
Walter Douglas Brown, Beaumont, Texas
Fred W. Bush, Rochester, N. Y.
Nicholas Boddie Cannady, Dothan, Ala.
Charles Rowse Dengler, Jackson, Mich.
R. Bruce Eldredge, Omaha, Neb.
Edward Porter Essertier, Hackensack, N. J.
George Julius Feldstein, Pittsburgh, Pa.
Alfred Elias Fischer, New York, N. Y.
Edward O. Fitch, Houston, Texas
James LeRoy Foster, Pittsburgh, Pa.
Hugh C. Graham, Tulsa, Oklahoma
Theodore P. Herrick, Cleveland, Ohio
George Russell Irving, New York, N. Y.
Sidney David Kramer, Brooklyn, N. Y.
Alfred Gustav Langmann, New York, N. Y.
George P. Laton, Los Angeles, Calif.
Mathilde Loth, New York, N. Y.
Mary Schwartz Newman, Brooklyn, N. Y.
Maurice J. Searle, Tulsa, Okla.
Harry M. Shapiro, New York, N. Y.
Edwin August Socola, New Orleans, La.
Edwin B. Weldon, Bridgeport, Conn.

Book Review

The Adopted Child. ELEANOR G. GALLAGHER, New York, 1936, Reynal and Hitchcock, p. 291. Price $2.50.

This is a disappointing book. As a "first book" on an important subject frequently brought to the pediatrician for discussion, it merits more of a review than the book inherently justifies. According to the cover blurb, it is a "complete book" for the general reader, as well as a "handbook" for social workers, adoption agencies, etc. It fails to fulfill in a satisfactory way any one of these purposes, let alone all. There are a number of excellent chapters, as the historical introduction and the summary of state laws relating to adoption in the appendix. Rather than the sound critical discussion which we are led to expect, the book as a whole turns out to be a somewhat emotionally biased special plea for the immediate separation of the illegitimate child from the mother, its immediate placement in an adoption nursery, and its placement into the adopting home when the baby is a few weeks old. There is much to be said in favor of this, but there is another viewpoint held by many intelligent and experienced people. Rather than critically presenting the other viewpoint, which should be done in a "complete book" on the subject of adoption, the author indulges in an uncalled for tirade against trained social workers and cites a few stupid actions of trained workers to prove their incompetence as a whole, simply because they disagree with the author's viewpoint—a fallacious and silly argument, as an equal number of stupid actions could be cited in regard to volunteer workers. Since some trained workers do not agree with the author's views and are responsible, in her opinion, for laws requiring maternal nursing for a few months, away with the whole tribe of them. Since intelligence tests are not available for young infants, the author attempts to show intelligence tests are of no value and simply displays a rather limited appreciation of their value and functions. By a few citations from literature she attempts to show that artificial feeding is the equivalent or even superior to maternal nursing. Thus the book becomes a special plea to uphold a viewpoint rather than a sound balanced discussion of the subject of adoption.

We are not informed as to the author's training, qualifications, and connections, except that we are told that she has had many years of experience in adoption work. The reviewer would hazard from the text that it has been in connection with the Cradle in Chicago. The excellent work of the Cradle is well known and scarcely needs the defensive attitude of the author. She further refers to the splendid work of Dr. Chapin and his wife in New York and the Spence organization, and then rather naïvely remarks that, although there are many other adoption nurseries scattered throughout the United States, she is unfamiliar with them. Excellent as the work of the Cradle undoubtedly is, it scarcely gives a broad enough background to cover the entire field of adoption with its many problems. The chief criticism against the adoption nurseries is that so far they have not taken advantage of their unique opportunity to make a careful critical scientific study of the development of the infants they have placed. Such a study would do more to show the value, or weakness, of the ideas the author defends than these many pages of personal opinion.

The value of giving in detail the Dick technic is decidedly questionable in a book for the parent or general reader. Physicians will agree with the author that the

child should be told it is adopted. The child, however, should have been told long before he could have understood the "precious" letter with which the author concludes the discussion of this topic.

The book is neither fish, flesh, nor fowl. If the emotionalism and non-germane controversial matter had been omitted and the title changed to "Adoption Nurseries" the book would have a place. But labeled as a "complete book" on the subject of adoption, it goes under false colors, and the reviewer feels it an unwise book for physicians to recommend to uncertain-minded and noncritical parents who are considering the problem of adoption.

Errata

In the article by Martha M. Eliot et al. entitled "A Study of the Comparative Value of Cod Liver Oil, Viosterol, and Vitamin D Milks in the Prevention of Rickets and of Certain Basic Factors Influencing Their Efficacy" in the September issue, the following corrections should be made.

On page 361 the last sentence above the illustration should appear as the last sentence of the first footnote.

On page 363 the following paragraph should be inserted after line 11:

"It should be pointed out that the incidence of rickets among the colored infants is consistently lower than among the white infants when the total groups given the different types of antirachitic agents are considered and that the same tendency exists with few exceptions at the different dosage levels for each agent."

On page 371 the footnote to Table X should read:

"Code: A_1-, B_1-, very slight," etc.

In the article, "The Problem of Dental Caries With Relation to Bacteria and Diet," by Philip Jay, M.S., D.D.S., which appeared in the June, 1936, issue of the JOURNAL, on page 729, line 44, the word "negative" should be "positive"; thus the sentence should read: "It was subsequently observed that the same proportion of caries-free individuals contained *L. acidophilus* agglutinins in the blood serum, whereas 70 per cent of the susceptible persons tested yielded positive skin tests and contained either no demonstrable acidophilus agglutinins or else agglutinin titers which were much lower than was ordinarily found in the caries-free."

In the article, "The Premature Infant," by William W. Swanson, M.D., Vernon E. Lennarson, M.D., and Fred L. Adair, M.D., which appeared in the July issue of the JOURNAL, the reference to Dr. Blackfan on page 15, line 41, is incorrect. His name should not have been mentioned in connection with the treatment by injecting whole blood intramuscularly.

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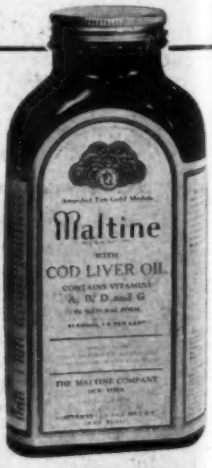

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